

WORLD HEALTH ORGANIZATION
MONOGRAPH SERIES

No. 27

CHEMOTHERAPY OF MALARIA

CHEMOTHERAPY OF MALARIA

SIR GORDON COVELL, C I E , M D

*Adviser on Malaria, Ministry of Health
Director, Malaria Laboratory, Horton Hospital, Epsom, Surrey, England*

G ROBERT COATNEY, Ph.D.

*Laboratory of Tropical Diseases, National Microbiological Institute,
National Institutes of Health, Bethesda, Md , USA*

JOHN W FIELD, C M G , M D

*Director, Institute for Medical Research,
Kuala Lumpur, Federation of Malaya*

JASWANT SINGH, M B , Ch B , D P H , D T M & H.

*Director, Malaria Institute of India,
Delhi, India*



WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

1955

NOTE

*Authors alone are responsible for views
expressed in the Monograph Series of the
World Health Organization*

The mention of manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature which are not mentioned. Proprietary names of such products are distinguished by an initial capital letter.

CONTENTS

	Page
Introduction	7
Chapter 1 Definition of terms and historical review	9
Definition of terms	9
Historical review	10
Chapter 2 The rationale of malaria chemotherapy	15
The chemical approach	15
The biological approach	23
Chapter 3 Individual compounds in common use	32
Quinine	32
Primaquine and other 8-aminoquinolines	37
Mepacrine	39
Chloroquine and other 4-aminoquinolines	43
Proguanil	46
Pyrimethamine	51
Chapter 4 Drug resistance in malaria	54
Resistance to the common antimalarial drugs	57
Proguanil resistance	59
Cross resistance	64
Origin and mechanism of drug resistance	65
Commentary	67
Chapter 5 The clinical use of antimalarial drugs	69
The aims of malaria chemotherapy	70
The confusions of dosage	72
The malaria patient	74
The symptomless carrier	85
Individual drug prophylaxis	86
Collective drug prophylaxis	89

	Page
Annexes	
Annex 1 Summary of suggested dosage	97
Annex 2 Base-content of tablets	99
Annex 3 Physical data regarding salts	100
Annex 4 Synonyms of antimalarial drugs	101
Selected bibliography	103
Index	119

INTRODUCTION

At its fourth session, held in Kampala, Uganda, in December 1950, the Expert Committee on Malaria of the World Health Organization expressed the opinion that it was desirable to bring together for the benefit of the medical profession factual information on the properties of antimalarial drugs, and advised the appointment of a drafting committee to undertake the task. In accordance with this recommendation, a committee was appointed with the following members: Sir Gordon Covell (Chairman), Dr G. Robert Coatsy, Dr John W. Field, and Lieutenant Colonel Jaswant Singh.

The fact that the four members of the committee are resident in countries as far distant from one another as England, the United States of America, Malaya, and India has necessarily delayed the completion of the work. It has not been possible for the entire committee to meet at any one time during the preparation of the text, but the Chairman has been able to hold personal discussions from time to time with Dr Coatsy and Dr Field and has maintained contact with Lieutenant Colonel Jaswant Singh by correspondence.

The committee wishes to acknowledge with thanks the assistance received from Dr W. Clark Cooper and Dr Howard W. Bond, USA, Dr T. Wilson and Dr J. F. B. Edeson, Malaya, and Dr A. P. Ray and Dr H. L. Bami of the Malaria Institute of India, Delhi.

CHAPTER 1

DEFINITION OF TERMS AND HISTORICAL REVIEW

Definition of Terms

The terminology followed in this study is in conformity with that suggested in the monograph *Malaria terminology*,¹ issued by the World Health Organization in 1953, viz

Blood schizonticide * a drug which acts on asexual parasites in the blood

Tissue schizonticide a drug which acts on asexual parasites in the tissues

- (a) *primary tissue schizonticide* a drug which acts on pre-erythrocytic (primary exoerythrocytic) forms,
- (b) *secondary tissue schizonticide* a drug which acts on secondary exoerythrocytic forms

Gametocytocide a drug which acts on the sexual forms of the parasite

Sporonticide a drug which acts on the sporogonic forms in the mosquito

Suppression implies the prevention of clinical symptoms by action on asexual parasites in the blood. It may be *temporary*, that is, operative only while the drug is being taken, or *permanent*, denoting that no attack will supervene even after the drug has been discontinued

Clinical cure indicates that the immediate symptoms of an attack have been relieved and that the patient has apparently recovered

Radical cure implies elimination of the parasite from the body, whether by natural recovery or as the result of treatment

Suppressive cure implies radical cure brought about while the patient is receiving suppressive medication

Spontaneous recovery is a term applied to clinical or radical cure brought about by nature, in the absence of specific medication

The word *prophylaxis* is commonly used for any method of protection from disease and, therefore, when applied to chemotherapy, it should

* This word is sometimes spelt *schizonticide* which is etymologically incorrect. It is generally accepted that if the first element of a compound word is Greek the letter 'o' is inserted before the suffix. If Latin the letter 'i'.

properly be designated *drug prophylaxis*. When applied to a community, the term *collective drug prophylaxis* is used, when to an individual, the term *individual drug prophylaxis*. *Clinical drug prophylaxis* is a term sometimes applied when the object is merely to prevent the occurrence of overt attacks during such time as the drug is administered. Action on the asexual erythrocytic forms is, however, already covered by the word suppression, and it is suggested that the word prophylaxis when applied to chemotherapy should be restricted to action on sporozoites or other pre erythrocytic forms (equivalent to the *true causal or causative prophylaxis* of James)

Names of antimalarial drugs ending with "in(e)" are written with an "e" by some authors and without an "e" by others. For the sake of uniformity, in this monograph all such words, unless they are trade names, are written with an "e", for example, chloroquine, amodiaquine, pamaquine, mepacrine, primaquine. In proprietary names of drugs a capital is used for the initial letter, in non proprietary names the initial letter is given in lower case.

Historical Review

Before the outbreak of the first World War, the only specific antimalarial drugs known were the cinchona alkaloids, of which the most commonly used was quinine.

Cinchona is the name given by Linnaeus to a family of plants indigenous to the eastern slopes of the Andes in memory of the Countess of Chinchon, wife of an early Viceroy of Peru, to whom legend attributes the introduction of the bark to Europe. Historical evidence does not support this story, but it is a fact that the bark of the *quina quina* tree, now known as cinchona, was introduced into Europe from South America by the Spaniards about the year 1640, and was used in Spain and Italy for the treatment of fevers from that time onward. Powdered bark had reached England by 1655 and was prescribed as such for the treatment of intermittent fevers for the next 200 years. It was used in North America during the War of Independence by the troops of both the contending armies.

The bark is said to have been introduced into India as early as 1657. During the latter half of the 18th century it was used extensively in that country, where it was popularized by the surgeons of the numerous ships trading in eastern waters. Dr. James Lind treated over 400 cases of intermittent or remittent fever in Bengal with cinchona bark in the year 1765 with excellent results. In the first half of the 19th century, cinchona passed through a phase of unpopularity in India, principally due to the malign influence of a certain Dr. Johnson, a naval surgeon, who visited Calcutta in 1804. He treated his first fever patient with cinchona bark and failed

to effect a cure. He bled and purged his second patient, who recovered, and thenceforth advocated a line of treatment of which the main feature was drastic purgation, salivation, and venesection. After a brief sojourn in India he returned to England, where he published a treatise on tropical diseases in which the administration of cinchona bark as a remedy for malaria was vehemently condemned. As a result, the use of the bark in India was practically abandoned, and for many years it was used merely as a tonic, in minute doses, after the subsidence of the fever. At this period as much as from 800 to 900 grains (50-60 g) of calomel were commonly prescribed for the treatment of a single attack of malaria.

From about the middle of the 19th century, the popularity of cinchona bark was re-established, largely through the influence of Edward Hare, who came to India in 1839 and was in medical charge of British troops in the Burmese War and during the siege of Delhi at the time of the Indian Mutiny. At this time the use of cinchona bark for malaria was frowned upon by the authorities, but Hare came across some of the old writings of James Lind, extolling its virtues, and decided to give it a trial. Over a period of nine years he treated some 7,000 cases of fever, with a mortality of less than $\frac{1}{2}\%$.

In 1820, quinine and cinchonine were isolated from the bark by two French scientists, Caventou and Pelletier. The dominant position subsequently attained by quinine in the treatment of malaria as compared with the other alkaloids of cinchona was largely due to the fact that it was the first to be isolated. In point of fact there is little difference as regards antimalarial properties between it and the three other principal alkaloids present.

Cinchona cultivation was established in Java by the Dutch in 1854, with seedlings brought from Bolivia and Peru by the botanist Hasskarl. In 1860, the British geographer Clements Markham obtained seeds from Peru, from which plantations were stocked in India and Ceylon, where the industry flourished for a while, but during the period 1880-90 reckless over production led to a fall in prices which proved ruinous. The planters in Java managed to survive the slump, and at the outbreak of the second World War about 97% of the world's supply of quinine came from that country.

The evolution of the synthetic antimalarials now in use makes an interesting story.⁶ Quinine is an effective drug for treatment of the clinical attack in most malarial infections, and it is doubtful whether any of the synthetic antimalarials would have been evolved but for the occurrence of the two World Wars. The fact that the Germans were cut off from all sources of quinine during the first World War was the stimulus which inspired the intensive search for synthetic substitutes which resulted in the

production of Plasmochin (now known as pamaquine) and later of Atebrin (now known as mepacrine). When this work was planned in the early 1920s, all attempts to synthesize quinine had failed, this was finally accomplished in 1944.³² But Guttman & Ehrlich,³⁴ in 1891, had discovered that methylene blue effectively stains malaria parasites and had tried the dye on patients suffering from vivax malaria, some of whom were relieved of their symptoms. The results were not sufficiently impressive to warrant the substitution of methylene blue for quinine, but they were destined to play an important part in shaping the course of subsequent researches.

In their work at Elberfeld,³⁵ the Bayer research chemists were greatly helped by a technique of testing antimalarial compounds in canaries infected with *Plasmodium relictum*, this system for evaluating compounds was introduced by Roehl in 1924. With Ehrlich's early observations in mind, they introduced a basic side chain into the formula of methylene blue, an easier procedure than effecting similar alterations in the quinine structure. One of the resulting compounds showed considerable activity against bird malaria. The next step was to attach various side chains to the quinoline nucleus, which is present in quinine. This line of approach finally resulted in the synthesis of pamaquine, which in 1925 was selected for clinical investigation from a large number of allied compounds. Pamaquine thus became the first synthetic quinoline compound to exhibit effective action against human malaria parasites, and the first drug of any sort with a destructive effect on the gametocytes of *P. falciparum*.

Although pamaquine has remarkable antimalarial properties, it was unsuitable as a therapeutic agent in several respects, the most important being its relatively high toxicity and the fact that it has little action on the asexual erythrocytic forms of *P. falciparum*. The German scientists accordingly embarked on further studies. They attached the basic side-chain which had been evolved for pamaquine to other heterocyclic nuclei, and in 1930 finally produced the acridine compound now known as mepacrine. This proved to be relatively non toxic and was the first synthetic drug with a definite destructive action on the asexual blood forms of *P. falciparum*. Approximately 12,000 different compounds were tested in the course of this work.

After preliminary tests on human malaria in Germany, pamaquine and mepacrine were subjected to an extensive series of field trials in various parts of the world under the auspices of the League of Nations. These trials, made in Algeria, Italy, Malaya, Roumania, and the USSR, brought clear and decisive proof of the high suppressive action of mepacrine in all forms of human malaria, but left some uncertainty as to the possible toxic effects of long-continued administration. Sinton & Bird³¹ in India made the unexpected discovery that pamaquine caused a marked reduction in

the relapse rate of vivax malaria—a finding of fundamental importance in subsequent researches on the 8 aminoquinolines. The protective properties of both pamaquine and mepacrine were studied by James and his colleagues in England. Pamaquine proved to be a causal prophylactic against *P. falciparum* and a partial causal prophylactic in vivax infections, though only at a dosage dangerously high for routine use. Mepacrine in a daily dosage of 100 mg was shown to be an effective suppressant for both vivax and falciparum infections, but at that time fears were expressed that this amount taken over an extended period might exert a harmful action.

The Germans went on to synthesize two other compounds, Resochin (chloroquine) and Sontoquin (sontoquine). Chloroquine was synthesized as early as 1934, but after a few human tests it was discarded on the ground that it was too toxic. Sontoquine, with its extra CH_3 group, was later produced in an attempt to neutralize these effects, and was undergoing field trials when the second World War broke out in 1939.

In the second World War, the Allies in their turn were cut off from the main sources of quinine when the Japanese overran Indonesia, and an enormous volume of research on antimalarials was undertaken on both sides of the Atlantic. In the United States of America an intensive investigation of the absorption, distribution, excretion, and metabolic transformation of mepacrine was undertaken. By mid 1943, it was shown that the drug was extensively localized in the tissues and that its effectiveness was a function of the concentration in the plasma. This information led to the adoption of improved dosage schedules and its general acceptance as an effective therapeutic agent in the management of malaria. The properties of mepacrine were explored, though on a very much less extensive scale, in the United Kingdom.

In Australia, during the period 1943-5, an extensive series of tests, in which more than 800 volunteers from military units took part, was conducted by an Army medical research team.⁷ These tests confirmed and amplified the earlier work on the suppressive value of mepacrine, and also proved that a daily dose of 100 mg of the drug could be continued for an indefinite period without serious ill-effects. It was the routine use of mepacrine as a suppressant, based on these findings, which enabled the Allied armies in the south west Pacific and south-east Asia commands to be maintained in a fighting condition at a time when the Japanese troops opposing them were gravely hampered by malaria casualties.

The French in North Africa studied the properties of ontoquine, established its high antimalarial activity, and found that it was well tolerated. Following the occupation of North Africa by the Allies, this information became available to the United States investigators, who synthesized a large series of 4-aminoquinoline derivatives, nine of which were given limited

production of Plasmochin (now known as pamaquine) and later of Atebrin (now known as mepacrine). When this work was planned in the early 1920s, all attempts to synthesize quinine had failed, this was finally accomplished in 1944.²² But Guttman & Ehrlich,¹⁴ in 1891, had discovered that methylene blue effectively stains malaria parasites and had tried the dye on patients suffering from vivax malaria, some of whom were relieved of their symptoms. The results were not sufficiently impressive to warrant the substitution of methylene blue for quinine, but they were destined to play an important part in shaping the course of subsequent researches.

In their work at Elberfeld,²³ the Bayer research chemists were greatly helped by a technique of testing antimalarial compounds in canaries infected with *Plasmodium relictum*, this system for evaluating compounds was introduced by Roehl in 1924. With Ehrlich's early observations in mind, they introduced a basic side chain into the formula of methylene blue, an easier procedure than effecting similar alterations in the quinine structure. One of the first investigations in the history of malaria chemotherapy was the investigation from a large number of allied compounds. Pamaquine thus became the first synthetic quinoline compound to exhibit effective action against human malaria parasites, and the first drug of any sort with a destructive effect on the gametocytes of *P. falciparum*.

Although pamaquine has remarkable antimalarial properties, it was unsuitable as a therapeutic agent in several respects, the most important being its relatively high toxicity and the fact that it has little action on the asexual erythrocytic forms of *P. falciparum*. The German scientists accordingly embarked on further studies. They attached the basic side-chain which had been evolved for pamaquine to other heterocyclic nuclei, and in 1930 finally produced the acridine compound now known as mepacrine. This proved to be relatively non-toxic and was the first synthetic drug with a definite destructive action on the asexual blood forms of *P. falciparum*. Approximately 12,000 different compounds were tested in the course of this work.

After preliminary tests on human malaria in Germany, pamaquine and mepacrine were subjected to an extensive series of field trials in various parts of the world under the auspices of the League of Nations. These trials, made in Algeria, Italy, Malaya, Roumania, and the USSR, brought clear and decisive proof of the high suppressive action of mepacrine in all forms of human malaria, but left some uncertainty as to the possible toxic effects of long-continued administration. Sinton & Bird²¹ in India made the unexpected discovery that pamaquine caused a marked reduction in

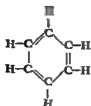
the relapse rate of vivax malaria—a finding of fundamental importance in subsequent researches on the 8 aminoquinolines. The protective properties of both pamaquine and mepacrine were studied by James and his colleagues in England. Pamaquine proved to be a causal prophylactic against *P. falciparum* and a partial causal prophylactic in vivax infections, though only at a dosage dangerously high for routine use. Mepacrine in a daily dosage of 100 mg was shown to be an effective suppressant for both vivax and falciparum infections, but at that time fears were expressed that this amount taken over an extended period might exert a harmful action.

The Germans went on to synthesize two other compounds, Resochin (chloroquine) and Sontochin (sontoquine). Chloroquine was synthesized as early as 1934, but after a few human tests it was discarded on the ground that it was too toxic. Sontoquine, with its extra CH_3 group, was later produced in an attempt to neutralize these effects, and was undergoing field trials when the second World War broke out in 1939.

In the second World War, the Allies in their turn were cut off from the main sources of quinine when the Japanese overran Indonesia, and an enormous volume of research on antimalarials was undertaken on both sides of the Atlantic. In the United States of America an intensive investigation of the absorption, distribution, excretion, and metabolic transformation of mepacrine was undertaken. By mid 1943, it was shown that the drug was extensively localized in the tissues and that its effectiveness was a function of the concentration in the plasma. This information led to the adoption of improved dosage schedules and its general acceptance as an effective therapeutic agent in the management of malaria. The properties of mepacrine were explored, though on a very much less extensive scale, in the United Kingdom.

In Australia, during the period 1943-5, an extensive series of tests, in which more than 800 volunteers from military units took part, was conducted by an Army medical research team.² These tests confirmed and amplified the earlier work on the suppressive value of mepacrine, and also proved that a daily dose of 100 mg of the drug could be continued for an indefinite period without serious ill effects. It was the routine use of mepacrine as a suppressant, based on these findings, which enabled the Allied armies in the south west Pacific and south-east Asia commands to be maintained in a fighting condition at a time when the Japanese troops opposing them were gravely hampered by malaria casualties.

The French in North Africa studied the properties of ontoquine, established its high antimalarial activity and found that it was well tolerated. Following the occupation of North Africa by the Allies, this information became available to the United States investigators, who synthesized a large series of 4-aminoquinoline derivatives, nine of which were given limited

Graphic formulaebenzene
ringpyridine
ringpyrimidine
ringquinoline
ringacridine
ring

Certain arsenical compounds, such as Stovarsol and Salvarsan, which have some action in vivax malaria, are benzene derivatives. The quinoline ring has much greater importance, and is the basis of the principal cinchona alkaloids and of the 4-amino- and 8-aminoquinolines. The acridine ring is the basis of mepacrine, chloroquine may be regarded as mepacrine with one ring removed, sontoquine and amodiaquine are modifications of chloroquine. Quinine is a 6-methoxyquinoline, while pamaquine, pentaquine, isopentaquine, and primaquine are 6-methoxy-8-aminoquinolines, that is, they are quinoline derivatives with a methoxy or amino group at the sixth or eighth position of the quinoline nucleus, counting from the nitrogen atom. In proguanil, the benzene ring is attached to a biguanide chain, pyrimethamine is a substituted pyrimidine.

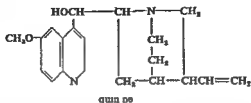
Cinchona alkaloids

Cinchona contains more than 20 alkaloids, but only four are of importance: quinine, quinidine, cinchonine, and cinchonidine. Cinchona febrifuge and totaquine are mixtures of alkaloids derived from the bark, the difference between them being that samples of the former may vary in composition, while in the latter the percentage of total crystallizable alkaloids and the quinine content must conform to a prescribed standard.

Chemically, quinine is a compound of complex molecular structure, visualized as being made up of three parts: the quinoline component (6-methoxyquinoline), the quinuclidine part (a complex ring with an attached vinyl group), and the connecting link (a hydroxylated methylene

group) Quinidine is an optical isomer of quinine, cinchonine and cinchonidine are optical isomers lacking the methoxy group

Graphic formula

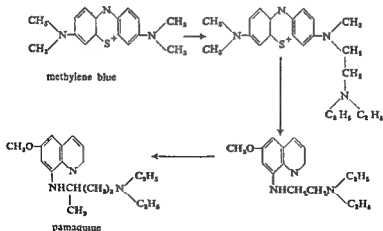


Various minor modifications of quinine have been studied in an attempt to evolve more active compounds but none of them has proved of practical value for the treatment or prophylaxis of human malaria

8 aminoquinolines

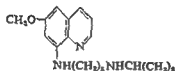
Mention has already been made of the early German researches in which methylene blue was shown to have some inhibitory effect on plasmodia. Schulemann and his colleagues at Elberfeld²³ found that by replacement of one of the methyl groups of methylene blue with a basic dialkylaminoalkyl group antimalarial activity was considerably enhanced. It seemed likely that the activity of the quinoline nucleus present in quinine might also be increased by the introduction of a similar basic side chain. It was by this line of reasoning that, in 1924, pamaquine was evolved.

Graphic formulae

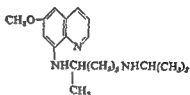


Pentaquine, *isopentaquine*, and *primaquine*, evolved as the result of re-examination of the 8 aminoquinolines in the United States of America during and after the second World War, differ from pamaquine in the type of alkylamino chain attached to the 6-methoxyquinoline ring

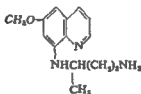
Graphic formulae



pentaquine



isopentaquine

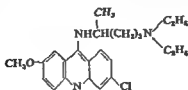


primaquine

9-aminoacridines

Mepacrine is an acridine dye, in which the quinoline ring is broadened to form the acridine. In the hope of decreasing toxicity, the German scientists replaced the quinoline ring of pamaquine by the acridine, which is relatively closely related to quinoline. By introducing the chlorine atom and a methoxy group into the acridine ring they finally produced mepacrine, in which the side chain is opposite the ring nitrogen as in quinine. It has been suggested that the activity of mepacrine is due to the capacity of the molecule to exhibit a form of tautomerism involving the lability of a hydrogen atom which can assume two alternative positions in the molecule

Graphic formula

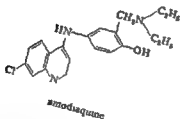
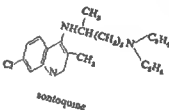
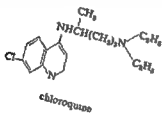


mepacrine

Studies carried out in Germany on this group of compounds followed the work on pamaquine and mepacrine in logical sequence. The mepacrine molecule was broken down into its constituent parts in an attempt to throw further light on the relationship between chemical structure and antimalarial activity. The removal from mepacrine of the methoxy bearing ring gave rise to chloroquine (originally known as Resochin). As already noted, sontoquine differs from chloroquine in having an extra methyl group on the quinoline nucleus.

Another member of the group, amodiaquine (Camoquin), in which the alkylamino side chain is replaced by a substituted anilino group, has also proved to be an effective blood schizonticide. These three drugs, together with mepacrine and quinine, all bear a structural similarity to one another. All except mepacrine are quinolines, and mepacrine may be regarded as containing the quinoline nucleus, and all have side chains opposite the ring nitrogen. It is probable that they all have a similar fundamental action against malaria parasites.

Graphic formulae



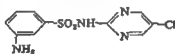
Sulfonamides

Since Diaz de León ⁶ in 1937 first claimed to have successfully treated cases of vivax malaria with a sulfa compound, many of these have been tested against avian, simian, and human malaria. Although none of the

group has proved of practical value in the chemotherapy of malaria, these studies have helped to elucidate a number of problems and have served as a guide in the synthesis of other compounds. Sulfanilamide will cure blood-induced knowlesi malaria, and many other derivatives of sulfanilamide, such as *p*-aminobenzenesulfonamide, act as true causal prophylactics against *Plasmodium* while the fact that the antimalarial activity is due to the *p*-aminobenzenesulfonamide group by *p*-aminobenzoic acid has shed light on the metabolic requirements of plasmodia generally.

One of the sulfonamides—metachloridine, which is structurally similar to sulfadiazine—is said to be active against quartan malaria, but against falciparum infections it has proved ineffective.

Graphic formula



metachloridine

Biguanides

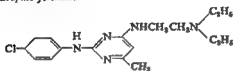
The work which led to the recognition of the antimalarial properties of this group of drugs began with the investigation by Curd, Davey & Rose^{66a} of certain pyrimidine derivatives, prompted by a consideration of the antimalarial activity of the pyrimidine-substituted sulfanilamides. A second reason for studying the pyrimidines was the similarity between the formulae of mepacrine and riboflavine, it was thought that the activity of mepacrine might be due to a competition with riboflavine for certain enzyme systems in the malaria parasite. A third reason was the characteristic of resonance* possessed both by the pyrimidines and by mepacrine.

In these researches the first compound found to be really active against bird malaria was number 2666. This compound contains the substituted pyrimidine ring and an alkylamino group attached to a nitrogen atom, close inspection of the formula shows both extended and true amidine systems. Another compound, 3349, a guanidine derivative of 2666, is even richer in amidine groups, it was the first of the series to show activity against human malaria. This compound is capable of existing in several tautomeric forms, and it therefore seemed possible that a pyrimidine ring as such was not essential and could be substituted by a biguanide group, which is capable of similar tautomerism. Eventually, the highest activity

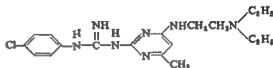
* Resonance is the phenomenon due to the transition from an electron configuration into another of the same spatial nuclear structure in a molecule. It is also called mesomerism and must not be confused with tautomerism in which the spatial arrangement of the atomic nuclei is different for the two tautomers.—Ed

in place of the more complex diethylaminoethyl group

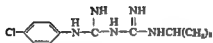
Graphic formulae



2066 RP



3349 RP



proguanil

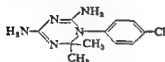
Diaminopyrimidines

Hitchings and his colleagues in the United States of America found that several substituted diaminopyrimidines are powerful antagonists of pteroylglutamic acid in cultures of *Lactobacillus casei*. The formal analogy between 2,4-diamino-5-*p*-chlorophenoxypyrimidine and proguanil and the finding that proguanil was also an antagonist of pteroylglutamic acid suggested that the pyrimidine compound might have antimalarial activity. A number of members of the group were studied and it was found that those with a 5 phenyl substituent were the most active. Substitution of a halogen or nitro group in the *para* position of the phenyl group was found to enhance activity. Substitution of an alkyl group in the 6 position of the pyrimidine also increased activity and in the case of 5-*p*-chlorophenyl derivatives a peak of activity was reached with the 6-ethyl compound (pyrimethamine) which proved 60 times as active as proguanil against *P. gallinaceum* and 200 times as active against *P. berghei*.

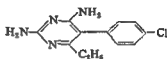
The active form of proguanil has been shown to be a metabolite which bears a striking resemblance to pyrimethamine. What was originally proposed as a purely formal analogy is now, therefore, to be regarded as

a real structural analogy. It is not surprising to find that the two compounds resemble one another closely in their antimalarial properties. There is also evidence that pyrimethamine itself may give rise to an active metabolite.

Graphic formulae



metabolite of proguanil

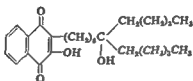


pyrimethamine

Naphthoquinones

Hydrolapachol and two other quinones have been found to possess some antimalarial activity and this has led to the synthesis of a number of other naphthoquinone derivatives. Although some members of the group have shown considerable activity against avian plasmodia their effect in human malaria has been generally disappointing presumably because they undergo rapid degradation in the human body. One of them, however, has been shown to have considerable resistance to metabolic deactivation, namely, Lapinone (M 2350), which has a hydroxylated C_{12} side chain. It has been claimed that this drug has definite suppressive activity against vivax malaria, but this finding needs confirmation.

Graphic formula



Lapinone

Organometallic compounds

It has been found that certain metallic compounds of arsenical nature (Salvarsan), neoarsphenamine (Neosalvarsan), Mapharsen, acetarsol (Stovarsol), and carbarsone—but although arrested development of the parasites and relief

of symptoms have been recorded in vivax infections, there has been no consistent diminution in the relapse-rate. Preparations of mercury, antimony, and bismuth have also been used for malaria with little success.

A bismuth compound—sodium bismuth thioglycollate, known as Thio Bismol—has been found useful for limiting vivax and malariae infections in the treatment of neurosyphilis by malaria therapy. It has an inhibitory action on the half and three quarter grown forms of the parasite and is used in vivax malaria for converting a quotidian type of fever into a tertian by destroying all except one generation of parasites. Neoarsphenamine has been used similarly in the Netherlands.

Antibiotics

Many antibiotics have been tested for antimalarial activity. Some action was shown by certain members of the group—for example, Chloromycetin, Aureomycin, Terramycin, and Fumagilin—but in no case have the results indicated that the drug would prove of practical value in the treatment or prophylaxis of malaria.

Miscellaneous

A number of amino alcohols derived from phenanthrene and naphthalene have been reported as showing antimalarial activity. One of the phenanthrene derivatives (SN 1796) has been tested against human malaria, but the response was poor.

Isolation of the active metabolite of proguanil has recently stimulated researches on substituted triazine derivatives and some of the compounds have been found more active than proguanil against experimental infections.

In the field of aminocresols and orthocresols, a compound designated SN 6771 has been found to display some activity against human malaria.

A number of pantothenic acid derivatives, thiocarbamates, diamidines, dicoumarins, dibenzamidines, hormones, vitamins and their analogues, sulfabiguanides, guanidines, thio derivatives, cinnolines, benzoacridines, and pyridoacridines have been tested, but in no case has any compound been discovered which could compete with the established antimalarial drugs.

The Biological Approach

Life cycle of the malaria parasite

More than 50 years have passed since the mode of transmission of malaria was proved and the existence of an asexual phase in man and a sexual phase in the mosquito was demonstrated. The latter was followed

out in full as early as 1898, but for many years one question regarding the former remained unanswered. What happens to the parasite during the period between the injection of the sporozoites into the body and the first demonstrable appearance of asexual forms in the peripheral blood?

Schaudinn,²² in 1902, reported that he had actually seen a sporozoite penetrate a red blood-cell, and this finding was at first generally accepted. But as the years went by and no one was able to repeat this observation, despite the most intensive search, it gradually became evident that Schaudinn had been mistaken, and that the parasite must undergo another phase of development in the body during the prepatent period, as indeed had been suspected by Grassi as early as 1900.

Raffaele,²¹ who described unpigmented parasites in avian malaria in 1934, was the first to recognize that these forms represented a definite phase of development in the tissues as distinct from that occurring in the blood. James & Tate,¹⁷ in 1937, described the exoerythrocytic schizogony of *P. gallinaceum* in the brain capillaries of the fowl, but the mystery of what happens during the period immediately after infection remained for a while unsolved.

In 1940, however, Shortt and his colleagues²⁰ in India and Mudrow²⁰ in Germany independently observed pre-erythrocytic forms of avian malaria during the prepatent period. This work was amplified in the United States of America by Huff & Coulston¹⁸ who, in 1944, described in detail the complete development of the pre-erythrocytic stages of *P. gallinaceum*.

Between 1943 and 1945, Fairley and his co-workers⁷ in Australia carried out some highly significant studies on human malaria by which it was shown that after infection by mosquito bites the sporozoites circulate in the blood for about half an hour, after which they disappear. This was proved by inoculating large quantities of blood into volunteers in whom malaria was produced if the blood was drawn from the donor within half an hour of infection. Subsequently the blood of the donor was innocuous for six days after inoculation with *P. falciparum* and for eight days after that with *P. vivax*.

At this time Shortt and Garnham in England had just begun a series of researches on mammalian malaria that were destined to achieve far-reaching results. In 1948, after massive infection by the bites of heavily infected mosquitos, which were afterwards ground up and injected parenterally into a rhesus monkey, pre-erythrocytic forms of *P. cynomolgi* were observed in a section of liver removed seven days later.²³

Subsequently, less mature stages of the parasite were found in the liver of other monkeys similarly infected, the earliest to date being in sections excised on the second day.²³ It has also been proved that in monkey

malaria exoerythrocytic parasites can persist in the liver after blood infection has been established. These forms are thought to be responsible for the phenomenon of late relapse in cynomolgi and vivax malaria. As such relapses are not encountered in falciparum infections, it is believed that such a phase does not occur in this type of malaria.

The demonstration of tissue forms of *P. cynomolgi* in the monkey made it practically certain that a similar phase exists in human malaria, and this was soon established for both *P. vivax* and *P. falciparum*. This work was carried out by Shortt and his team in London, in collaboration with the staff of Horton Malaria Laboratory.^{25, 26} In December 1953, Garnham and his co-workers succeeded in demonstrating pre-erythrocytic forms of *P. ovale* in the human liver.²¹ Two years earlier, Garnham²⁰ had demonstrated in the liver of a monkey pre-erythrocytic forms of *P. inui* which closely resembles *P. malariae* in all essential features. The existence of a pre-erythrocytic phase of *P. falciparum* has been confirmed by Jeffery and his colleagues¹⁹ in the United States of America.

The life-cycle of the malaria parasite may be summarized as follows. When an infective mosquito bites a new host, sporozoites are inoculated into the blood stream. There they circulate for about half an hour, after which they disappear. It is presumed that many of them are arrested in the liver, although the earliest stage of development in that organ has not yet been observed. As stated above, however, pre-erythrocytic forms of *P. cynomolgi* have been demonstrated as early as the second day after infection. The tissue schizont, as the parasite is now called, increases in size and divides to form thousands of minute merozoites. The cell envelope ruptures, setting free the merozoites into the surrounding tissues. Many of these probably attach themselves to red cells in the liver sinusoids, but it is believed that, except in falciparum malaria, some penetrate other liver cells and either remain dormant or repeat the cycle of schizogony. These are the forms to which late relapses in vivax malaria have been attributed.

The young merozoites which enter the blood stream are now called trophozoites. It is generally believed that the parasite actually penetrates the red cell, but some observers hold that it remains on the outer surface. The trophozoites increase in size and become schizonts. These ultimately rupture, discharging merozoites, which enter other red cells and repeat the process of schizogony. After a while certain merozoites are produced which become sexually differentiated as male and female gametocytes. Should a mosquito bite the host at this time the sexual forms are taken up and conjugate in the insect's stomach to form a zygote. This lengthens to become an ookinete or vermicle, which penetrates the stomach wall and comes to rest on the outer surface, where it is known as an oocyst. The cyst grows and divides into thousands of elongated

bodies called sporozoites. When the cyst ruptures, many of the sporozoites find their way into the salivary glands, whence they are injected into a new host when the mosquito next takes a blood meal.

Drug action in relation to different stages of the life cycle

In theory, a drug may act on the malaria parasite in any of the following ways: (1) against the sporozoites when they first enter the human body, (2) against the primary tissue or pre-erythrocytic forms of the parasite, (3) against the asexual parasites in their erythrocytic phase, (4) against the sexual parasites in their erythrocytic phase, (5) against the late exoerythrocytic or secondary tissue phase, to which the phenomena of latency and late relapse in vivax and possibly in quartan malaria have been attributed, and (6) against the sporogonic forms in the mosquito phase of the life-cycle.

The drugs which are known to act on the sporozoites are quinine, (d) the 8-aminoquinolines (pamaquine, primaquine), (e) the biguanides (proguanil), and (f) the diaminopyrimidines (pyrimethamine).

No drug yet tested has any demonstrable effect on the sporozoite stage of the malaria parasite. The cinchona alkaloids, aminoacridines, 4-aminoquinolines, and the biguanides have a powerful destructive action on the gametocytes of all species, but they have a powerful destructive action on the gametocytes of all species. They also act on the secondary exoerythrocytic forms of *P. vivax*, and it is in this respect that they have their greatest value. They have an inhibitory effect on the pre-erythrocytic forms of both *P. falciparum* and *P. vivax* but cannot be used for this purpose without risk of toxicity.

The biguanides and the diaminopyrimidines are the only drugs which can be used with safety against the pre-erythrocytic forms, and so far as is known they are fully effective only in *falciparum* infections. They have no apparent action on the sexual forms of *P. falciparum* in the peripheral blood, but both render these incapable of completing their development in the mosquito.

Antimalarial drugs may thus be placed in groups according to the stage of the life cycle on which they act, viz:

(1) *Drugs acting on pre-erythrocytic forms* (primary tissue schizonticides, causal prophylactics). For practical purposes, only proguanil and pyrimethamine come under this heading.

(2) *Drugs acting on asexual erythrocytic forms* (blood schizontocides *)

While most antimalarial drugs have some action on these forms, the only ones which are of practical value for treatment of the clinical attack are chloroquine and related 4-aminoquinolines, mepacrine, and quinine. These drugs are effective suppressants of all species of human malaria parasites, and will effect radical cure in most cases of falciparum infection. Proguanil and pyrimethamine are also effective suppressants, but are not sufficiently rapid in action for treatment of the clinical attack in a non immune subject.

(3) *Drugs acting on late exoerythrocytic forms* (secondary tissue schizontocides; anti-relapse drugs) The only compounds in this category known to be effective are the 8-aminoquinolines (pamaquine, primaquine).

(4) *Drugs acting on the sexual forms* (gametocytocides) Pamaquine and probably other 8-aminoquinolines have a powerful destructive action

on the sexual forms of *P. falciparum* and *P. vivax*. Quinine

the peripheral blood within a few days of treatment with these drugs.

(5) *Drugs acting on the sporogonic forms in the mosquito* (sporontocides) Proguanil and pyrimethamine come under this heading.

Pharmacological considerations

An enormous volume of research has been devoted to studies of the pharmacology of antimalarial drugs, but there are still many gaps left in knowledge of the subject, even in respect of the cinchona alkaloids. For the effective treatment of the clinical attack, an adequate concentration of the drug in the red blood-cells, where the parasites reside, is essential. The concentration attained in these cells by different drugs, however, shows wide variations. That of quinine may be as low as one-eighth of the concentration in the plasma. The low cell concentration attained by quinine as compared with other schizontocidal drugs is no doubt a reason why so much higher doses are required to produce the necessary effect.

Factors which affect the attainment and maintenance of an adequate drug concentration in the red cells include the rate of absorption of the drug from the alimentary canal, competition for the drug between the red cells and various body constituents, such as the plasma proteins and tissue cells, and the rate at which the body degrades and excretes it.

Mepacrine and the 4-aminoquinolines are rapidly absorbed and soon become localized in the tissues; degradation and excretion are slow and

* This term has been suggested to distinguish these drugs from those acting on tissue schizonts, but they are still commonly designated schizontocides without qualification.

consequently these drugs persist in the body for long periods. It is therefore necessary to administer a high initial, or loading dose, the red-cell concentration being kept at the required level thereafter by a lower maintenance dosage. It is interesting to note that the principle of giving a high loading dose of mepacrine, put forward by Shannon and his colleagues²¹ in 1944, to enhance the therapeutic effectiveness of the drug, has found general acceptance among clinicians, the principle applies equally well in the use of chloroquine and other 4-aminoquinolines.

Quinine and the 8-aminoquinolines are rapidly absorbed, but plasma concentrations fall very rapidly in both instances. It is therefore necessary to administer doses as high as possible and at frequent intervals, rather than a high loading dose followed by a lower maintenance dose.

Proguanil and pyrimethamine are active in very low concentrations, so

It is recognized, however, that there are other factors besides blood concentration to be taken into consideration. There is evidence, for instance, that proguanil and pamaquine, and probably also pyrimethamine, are not themselves active agents, but owe their efficacy mainly to a transformation within the body into active metabolites. Further details regarding the pharmacological action of individual drugs are given in chapter 3.

The varying response of different strains of the parasite

Infections produced by strains of the same species of malaria parasite from different geographical areas may show wide variations in pathogenicity, ability to develop in the mosquito host, relapse pattern, and immunological properties. It is not surprising therefore, that differences in their response to the action of a particular drug are sometimes encountered. More than 30 years ago, James and his colleagues observed that the amount of quinine required to control infections with Italian strains of *P. falciparum* was several times as great as that needed for the management of infections with a strain of the same species of parasite from India. In recent years, a number of similar instances have been recorded. Infections with a New Guinea strain of *P. falciparum* were successfully treated with proguanil by Fairley and his colleagues, whereas the same drug proved ineffective for radical cure of an infection with a strain of the same species of parasite imported to England from West Africa. In prophylaxis, however, the drug proved equally effective against either strain. Again, the Chesson strain of *P. vivax* from New Guinea was found to be more refractory to both quinine and mepacrine than the McCoy strain from the southern United States of America.

The Chesson strain, which is characterized by a series of relapses occurring at short intervals following the primary attack, was also found by Coatsy and his colleagues to be much more refractory to anti-relapse treatment with primaquine than the long term relapsing St Elizabeth strain originally encountered in the United States of America

The relapse rate in vivax malaria is closely related to the manner in which the primary attack is treated. Thus, with the Madagascar strain used in England for malaria therapy of neurosyphilis, if the patient is allowed to have a succession of 12 to 14 febrile paroxysms before treatment is begun, the relapse rate is about 50%, whereas, if an efficient blood schizonticide is administered early in the attack, the rate may reach 90% or even higher*

The immunity factor

Many persons of the Negro race and occasional individuals of other races are highly refractory to infection with vivax malaria. This is an example of *natural immunity*, as distinct from *acquired immunity*, which is the result of past or present infection

Tolerance is an acquired immunity contingent on and conditioned by the continued presence of the parasite in the host. A host with tolerance exhibits less reaction to a given quantum of infection, whereas one with natural immunity has an increased ability to limit the quantum of infection developed. *Premunition* is almost synonymous with tolerance, but has a greater connotation of immunity to superinfection with the same parasite

In malaria the immunity response is directed primarily against the asexual parasites in the blood, the tissue forms in the liver being completely protected from the cellulo humoral immunity response. An acquired immunity is most effective against infection with the same strain of parasite, but it may operate against heterologous strains to some degree

The efficacy of an antimalarial drug cannot be properly assessed until it has been subjected to carefully controlled experimentation on subjects who are completely non immune

Synergism

There are many examples in chemotherapy where the action of a particular drug is enhanced or reinforced by the concurrent administration of another. Sinton and his colleagues in India concluded that a combination of quinine with pamaquine was more effective for radical cure of vivax

* It is not suggested however that specific treatment of an overt malaria attack should be delayed on this account

infections than the action of either drug given separately. As the result of these findings it has generally been accepted that quinine has a synergistic action on the 8 aminoquinolines or on their active derivatives enabling them to destroy the late exoerythrocytic parasites more effectively and so prevent relapses. Recent observations in the United States of America on avian and simian malaria have, however, thrown some doubt on this theory. Coatney and his colleagues were unable to demonstrate synergism between quinine and the 8 aminoquinolines against gallinaceum infections, and Schmidt has been equally unsuccessful in experiments with *P. cynomolgi*, whose behaviour resembles that of the late relapsing strain of *P. vivax* in so many respects. These findings suggest that the two classes of 8 aminoquinolines act on the late tissue

of Korean vivax malaria among United States military personnel by the routine administration of primaquine alone.

Greenberg and his co-workers¹³ have shown that proguanil and sulfa diazine potentiate each other's action against *P. gallinaceum*, and have demonstrated a synergism between proguanil and *p*-aminobenzoic-acid antagonists which themselves act against gallinaceum infections.

Effect of drugs on plasmodium metabolism

The first researches undertaken on the subject of the effect of drugs on plasmodium metabolism were those of Christophers & Fulton,² who published results of their studies on the respiratory metabolism of *P. knowlesi* in 1938. Intensive investigations on the biochemistry of erythrocytic stages of malaria parasites were continued during the second World War, particularly in the United States of America. The metabolic activities of the parasites were found to resemble closely those of other organisms previously studied.

It was known that quinine has the property of inhibiting certain enzymes, and it seemed possible that the therapeutic effect of antimalarial drugs might be measured by their power to inhibit the respiration of malaria parasites. The quantitative effect of various compounds on the oxygen uptake of malaria parasites was therefore investigated and it was found that the inhibitory action was in some degree parallel with the therapeutic effect. Except in the case of certain naphthoquinones, however, the correlation between inhibition of respiration of a malaria parasite and therapeutic efficiency of a drug was poor.

A number of other researches have been planned with the object of discovering some vulnerable link in the metabolic chain and in the growth

requirements of malaria parasites which might provide a clue to the synthesis of more effective drugs

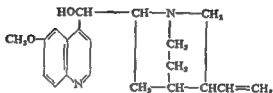
From studies on the respiration and carbohydrate metabolism of malaria parasites it is possible to indicate certain points where these processes are deranged by antimalarial drugs. There are also indications that certain vitamins, such as *p*-aminobenzoic acid, pantothenic acid, and folic acid, if deficient or in excess, may influence antimalarial action. Little is as yet known of the nitrogen requirements or nitrogen metabolism of malaria parasites, but it seems probable that while the parasite relies on the red cell for its protein metabolism, protein hydrolysis is linked up with oxidative processes. Further studies are necessary because the possible action of antimalarial drugs on protein metabolism can be explained on a satisfactory basis.

CHAPTER 3

INDIVIDUAL COMPOUNDS IN COMMON USE

Quinine *

Formula



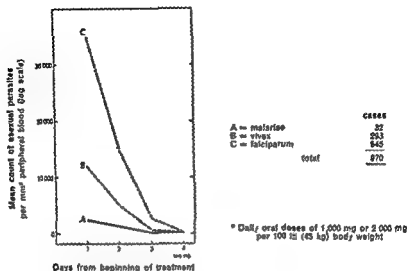
quinine 6 methoxy (5 vinyl 2-quinuclidyl)-4-quinol nemethanol

Activity in human malaria

- (a) Sporozoites
 - (b) Primary exoerythrocytic forms
 - (c) Asexual erythrocytic forms
- } Inactive Quinine is hence useless for *causal prophylaxis*
- (c) Asexual erythrocytic forms A highly active blood schizontocide in all forms of human malaria, and hence an efficient drug for clinical cure. With prolonged administration *radical cure* is often possible in falciparum infection, but seldom in vivax infection. For *suppression* and *suppressive cure* quinine is less efficient than mepacrine or the better known 4 amino quinolines.
- (d) Gametocytes Quinine has little gametocytocidal activity in falciparum malaria but is an effective gametocytocide in vivax and quartan malaria, for general *gametocytocidal prophylaxis* it is a poor drug.
- (e) Secondary exoerythrocytic forms Inactive Quinine is thus a poor drug for *radical cure* in vivax malaria when used alone, when combined, however, with certain of the 8 aminoquinolines a high cure rate is possible in vivax infection.
- (f) General The value of quinine in the treatment of malaria is attested by long experience. Safe to use, consistent in action on the schizontic blood forms, it may be used with confidence for the relief of symptoms in acute malaria, and, indeed, for the immediate treatment of severe

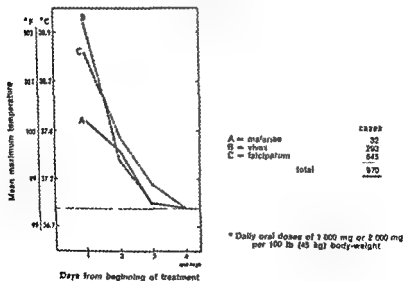
* See Selected bibliography No 33 39 (page 106)

FIG 1 EFFECT ON ASEQUAL PARASITAEMIA IN ACUTE MALARIA OF THERAPEUTIC DOSES OF QUININE DIHYDROCHLORIDE *



Unpublished data from Institute for Medical Research Federation of Malaya 1933-41

FIG 2 EFFECT ON FEVER IN ACUTE MALARIA OF THERAPEUTIC DOSES OF QUININE DIHYDROCHLORIDE *



Unpublished data from Institute for Medical Research Federation of Malaya 1933-41

falciparum infection, some authorities believe that quinine is unsurpassed by any of the new synthetic compounds. Its value as an adjuvant to the aminoquinolines for the radical cure of vivax malaria is discussed in chapter 5 (page 82).

Toxicity

Serious toxic effects from the clinical use of quinine are very rare, but the drug has its own characteristic side effects. Giddiness, deafness, ringing in the ears, tremors, and blurred vision may occur during the first few days of administration, particularly when the plasma level exceeds 12 mg per litre. These symptoms, collectively known as cinchonism, are seldom severe enough to interfere with treatment, they subside quickly when administration ceases and are never of serious import. Given intravenously, quinine lowers the blood pressure. Fatal collapse may occur as a result of intravenous injections administered too quickly in very severe infection.

Idiosyncrasy to quinine occurs, but is rare. Urticarial or erythematous rashes with intense itching, subcutaneous or submucous haemorrhages, oedema of the eyelids, mucous membranes, or lungs, and even collapse, have been known to follow a single dose. Excessive dosage may cause temporary blindness or deafness, possibly with permanent impairment of sight or hearing. Recovery from a single oral dose of 10 000 mg (150 grains) and death from a single dose of 16,000 mg (240 grains) have been reported.

Contraindications

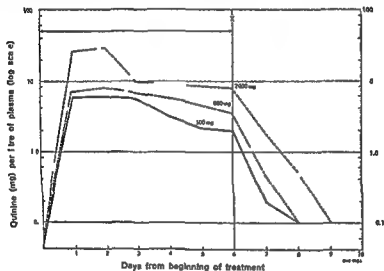
There are few contraindications to the use of quinine in the treatment of malaria. Patients with an idiosyncrasy to quinine must obviously be treated with some other drug, and a history or threat of blackwater fever is a clear indication for withholding quinine in favour of one of the synthetic compounds. The controversial question of quinine in pregnancy has lost its urgency with the modern developments in therapy, untreated malaria is more likely to induce abortion than is quinine, but most physicians will play for safety by using some alternative drug.

Absorption, elimination, plasma concentration

Quinine passes through the stomach unchanged and is quickly and almost completely absorbed from the upper intestinal tract to circulate as a base. The rate of absorption is not greatly affected by the route of administration, and the drug appears in the urine in an hour or less whether

given by the mouth or by intramuscular or intravenous injection. Quinine is quickly destroyed by the tissues or excreted unchanged in the urine, and little remains in the body 48 hours after the last dose. Peak concentrations in the plasma are reached from one to three hours after administration by mouth, the amount in the red cells being about one fifth of that in the plasma. A mean plasma concentration of 2.5 mg per litre is

FIG 3 CONCENTRATION OF QUININE (GROUP MEANS) IN PLASMA DURING TREATMENT WITH 500 mg, 1 000 mg AND 2 000 mg OF QUININE SULFATE DAILY FOR SIX DAYS



X = end of treatment

After Cooney et al.²⁰

probably necessary to reduce parasitaemia in acute vivax malaria, and

species the effective plasma level may depend on the strain of parasite

Dosage and route of administration

See chapter 5

Test for detection in body fluids

Quinine may be detected in the urine by Mayer's test

Mayer's reagent

Mercuric chloride	6,800 mg
Potassium iodide	24,900 mg
Distilled water	500 ml

Procedure

- (a) Add clear urine to each of two test tubes (cloudy urine should be shaken with kieselguhr and filtered)
- (b) To one tube add a few drops of acetic acid
- (c) To both tubes add a few drops of the reagent

Interpretation

- (a) If both tubes remain clear, the test is negative
- (b) If both tubes show turbidity, the presence of quinine is probable. Confirm by demonstrating the disappearance of turbidity on boiling the acidified urine in tube 2. Should the urine remain turbid the presence of albumin is probable. Filter hot to remove the albumin. Quinine precipitates as the filtrate cools.
- (c) If the acid tube alone shows turbidity, the presence of quinine, albumin, or both may be inferred. To identify quinine, boil and filter hot, as in (b). Precipitates due to quinine and albumin appear almost immediately. Sometimes turbidity develops slowly in the acid tube, when the presence both of quinine and albumin can be excluded. Precipitates which appear late may be ignored for the purpose of the test.

Cinchona mixtures

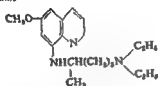
Mixtures of cinchona alkaloids have one advantage over quinine: they are cheaper. Their activity in the treatment of malaria is essentially the same: they cannot be used for injection and they are rather more likely to cause nausea or vomiting. According to the definition of the Malaria Commission of the League of Nations, totaquina (totaquine) is a mixture containing not less than 70% of crystallizable cinchona alkaloid, of which not less than 15% is quinine, nor should it contain more than 20% of amorphous alkaloids. It should not contain more than 5% of water, and the mineral ash-content should not exceed 5%, preferably 3%.

Salts in common use

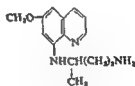
Sulfate, bisulfate, hydrochloride, and dihydrochloride, prescribed either in solution or in tablets or capsules

Physical data regarding salts

See Annex 3

Primaquine and Other 8-aminoquinolines**Formulae*

pamaquine 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline



primaquine 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline

Activity in human malaria

- (a) Sporozoites Probably inactive
- (b) Primary exoerythrocytic forms Active against these forms of *P. vivax* and *P. falciparum*, particularly the latter. Activity against these forms of *P. malariae* is not known.
- (c) Asexual blood forms Active against the asexual blood forms of *P. vivax* and *P. falciparum*, but only at a dosage dangerously high for routine use.
- (d) Gametocytes Highly active against the gametocytes of all species of human malaria parasite.
- (e) Secondary exoerythrocytic forms Highly active. Radical cure of vivax malaria is usually produced whether the drug is administered during a relapse or during latency. Data on similar presumed stages of quartan malaria are not available.
- (f) General The discovery in pamaquine of a drug which could act

* See Selected bibliography No. 40-53 (page 107)

asexual blood parasites, like that of the other 8-aminoquinolines, is effective only at dangerously high dosage has, however, precluded its use for treatment of the acute attack, though it has been used extensively for the prevention of relapse in vivax malaria, for which until recently it was the only drug available. It seems likely that primaquine, with its lower toxicity and greater effectiveness against fixed tissue stages of the parasite, will eventually supersede pamaquine for the radical cure of relapsing malaria. Studies are now in progress to investigate its effectiveness for prophylactic suppression.

Toxicity

At the recommended dosage, no symptoms of toxicity are likely. When include anorexia, nausea, and cramps, the passage of chest pain, and weakness.

In addition, there may be striking effects on the formed elements of the blood and the bone marrow, marked by leukopenia, anaemia, methaemoglobinaemia, and suppression of myeloid activity, with lesser effects on the heart and circulation. These manifestations disappear when the drug is withdrawn. The tendency for haemolytic reactions is increased in all the dark-skinned races.

Contraindications

Because the tendency for methaemoglobinaemia and granulocytic neutropenia, and probably for acute haemolytic anaemia, is potentiated by mepacrine, none of the 8-aminoquinolines should be administered concurrently with, or immediately following, treatment with mepacrine.

Absorption, elimination

All the 8-aminoquinolines are rapidly absorbed, elimination is accomplished entirely within 24 hours through metabolic conversions and excretion of the degradation products in the urine, only a very small amount is fixed in the tissues.

Dosage and route of administration

See chapter 5

Tests for detection in body fluids

Because of the rapidity of elimination and of the low dosages needed to effect cure, tests for plasma concentration of the 8-aminoquinolines are neither needed nor recommended.

Salts in common use

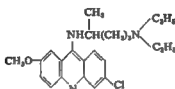
Primaquine diphosphate, pamaquine naphthoate and monohydrochloride

Physical data regarding salts

See Annex 3

Synonyms

See Annex 4

Mepacrine ***Formula**

mepacrine 6-chloro 2-methoxy 9-(4-diethylamino-1-methylbutylamino)acridine

Activity in human malaria

(a) Sporozoites - Probably inactive

(b) Primary exoerythrocytic forms Inactive against these forms of all species of malaria parasite

(c) Asexual blood forms Highly active against the asexual blood forms of all species Will produce *clinical cure* of all types of human malaria and *radical cure* of falciparum infection Mepacrine is an excellent *suppressive* agent against all species of human malaria parasite and in falciparum infection it can effect *suppressive cure* Morphological changes, marked by a distinctive clumping of the pigment, are characteristic of its action

(d) Gametocytes Mepacrine acts as a gametocytocidal agent against *P. vivax* and *P. malariae*, it is ineffective against the gametocytes of *P. falciparum*

(e) Secondary exoerythrocytic forms Inactive Mepacrine will not effect *radical* or *suppressive cure* of vivax malaria The effect on similar presumed stages of quartan malaria is unknown

* See Selected bibliography, No. 5471 (a) (page 109)

(f) General Mepacrine is superior to quinine in that (1) it has greater antimalarial activity against asexual blood parasites both as a suppressant and as a therapeutic agent, particularly against certain strains of *P. falciparum*, (2) its use is attended by a lower incidence of black-water fever, (3) it is a synthetic product and therefore supply is not affected by vicissitudes of nature or by geographical location. Even with these advantages the drug has certain limitations: (i) it dyes the skin and conjunctivae yellow and occasionally causes alarming, though transient, mental disturbances (see below), (ii) it must be given daily, or not less than twice weekly, for complete suppression of all types of malaria, (iii) adequate management of acute malarial attacks in non-immune subjects may require seven days of drug administration.

Toxicity

When administered initially at the recommended dosage, gastrointestinal distress may appear in the form of abdominal cramps, nausea, vomiting, and diarrhoea, but these symptoms disappear with continued administration of the drug. Mental symptoms varying from pronounced depression to extreme excitement or even mania may occasionally occur, but these disappear when the drug is withdrawn. Under humid tropical conditions cutaneous lesions (atypical lichen planus) may develop into a generalized exfoliating dermatitis. Aplastic anaemia has also been attributed to prolonged ingestion of mepacrine.

Contraindications

Apart from individual idiosyncrasy, syphilis affecting the central nervous system is the only contraindication to the use of mepacrine in the treatment of malaria.^{71*} Convulsive seizures have been recorded in such patients following its administration, and it is advisable, therefore, to use some other drug for the management of malaria in such cases.

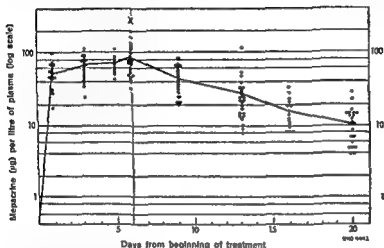
Absorption, elimination, plasma concentration

Absorption of the drug is rapid, elimination is slow, due to its pronounced affinity for the organs and tissues, where the concentration may reach several hundred times that found in the plasma. Only about 10% or less is eliminated in the urine daily, with the result that from three to four weeks are required for concentrations to drop below non-effective levels. Peak concentrations of 50-60 µg per litre in plasma are attained
When doses
plasma

Dosage and route of administration

See chapter 5

FIG 4 INDIVIDUAL CONCENTRATIONS AND GROUP MEANS OF MEPACRINE IN PLASMA DURING AND FOLLOWING 6-DAY THERAPEUTIC COURSES *



X = end of treatment

— mean concentration

• ... individual concentration

* 200 mg of mepacrine hydrochloride 4 times daily the first day followed by 100 mg of mepacrine hydrochloride 4 times daily for 5 days

After Cooper et al ²⁷

Tests for estimation in body fluids

(1) For estimation of mepacrine in body fluids, a single extraction procedure has been developed by Brodie et al ²⁸

Reagents

(a) 0.1 N NaOH

(b) Heptane — technical grade is purified by successive washings with 1 N NaOH, 1 N HCl, and water

(c) Iso-amyl alcohol, reagent grade

(d) Trichloroacetic acid solution 2,500 mg of the acid are dissolved in 100 ml of ethylene dichloride

Procedure

(a) Add 1.5 ml of biological fluid and an equal volume of 0.1 N NaOH to 15 ml of heptane in a 60-ml glass stoppered bottle

(b) Shake for 30 minutes. Allow the phases to separate, centrifuging if necessary

(c) Add 0.5 ml of *iso* amyl alcohol and mix with the heptane phase so as not to disturb the aqueous phase

(d) Transfer 10 ml of the heptane phase material to a fluorometer tube containing 1 ml of trichloroacetic acid solution. A blank of the heptane, *iso* amyl alcohol and the trichloroacetic acid solution is used for the setting of the fluorometer. If a reagent blank—namely, with water substituted for plasma or urine—is run, the reading should be the same as the blank set up with pure chemicals

Standards are prepared by extracting known amounts of mepacrine in the same manner as the biological sample. The computation of mepacrine concentration is by direct proportion

(2) A modification of the test, devised by Wats & Ghosh,⁷¹ has been found useful in Malaya

(a) To 10 ml of urine in a test tube add 1 ml of saturated solution of potassium carbonate

(b) To the alkalinized urine add 0.25 ml of amyl alcohol

(c) Thoroughly shake and put aside for a few minutes to allow the alcohol to separate

(d) Examine by ultra violet light for yellow fluorescence in the alcohol layer

The alcohol layer contains most of the mepacrine. When examined by ultra violet light, the extracted mepacrine fluoresces a vivid yellow. The test is extremely sensitive and reveals the presence of mepacrine in a dilution approaching one part in two and a half million.

Salts in common use

Dihydrochloride dihydrate, methane sulfonate

Physical data regarding salts

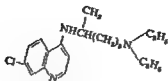
See Annex 3

Synonyms

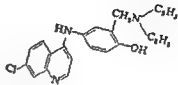
See Annex 4

Formulae

Chloroquine and Other 4-aminoquinolines *



chloroquine 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline



amodiaquine 7-chloro-4-(3-diethylamino-methyl-4-hydroxyphenylamino)quinoline

Activity in human malaria

- (a) Sporozoites Probably inactive
- (b) Primary exoerythrocytic forms Inactive in all types of malaria
- (c) Asexual blood forms Chloroquine and amodiaquine are highly effective against the asexual blood forms of all species of malaria parasite. They will produce clinical cure of all types of malaria parasite cure of falciparum infection. They are excellent suppressive agents against all species, such administration continued for from three to four weeks, results in suppressive cure of falciparum malaria. Morphological changes, marked by distinctive clumping of pigment, are characteristic of their action.
- (d) Gametocytes Chloroquine and amodiaquine act as gametocytocidal agents against *P. vivax* and *P. malariae*, they are ineffective against the gametocytes of *P. falciparum*.
- (e) Secondary exoerythrocytic parasites Inactive. They will not produce radical or suppressive cure of vivax malaria. The effect on similar presumed stages of quartan malaria is unknown.
- (f) General Chloroquine and amodiaquine are superior to mepacrine in that (1) they have greater activity as suppressive and therapeutic agents, fever is usually absent after 24 hours with elimination of patent parasitaemia in from 48 to 72 hours. (2) less frequent administration is required for effective results. (3) periods of latency are longer, (4) there is less tissue reaction following intramuscular administration, (5) they do not stain the skin or conjunctivae.

Sontoquine and other 4-aminoquinolines hitherto tested have proved less active than chloroquine or amodiaquine as regards antimalarial properties

* See Selected Bibliography, No 72-88 (page 109)

Toxicity

Toxicity is extremely low at doses ordinarily employed for therapy or suppression and although headache, pruritus, and blurring of vision have been reported following therapeutic doses, these symptoms usually disappear shortly after administration has been discontinued

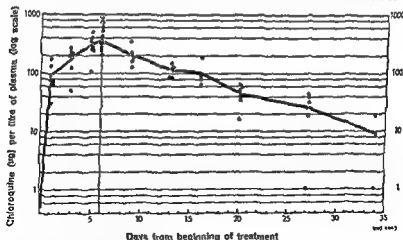
Contraindications

No contraindications have been reported to date

Absorption, elimination, plasma concentration

Absorption from the gastro intestinal tract is rapid and almost complete. These drugs are extensively localized in the tissues, from where they are metabolized and excreted slowly. On an equal dose basis, concentrations of chloroquine in the plasma are from 10 to 20 times higher and persist longer than in the case with mepacrine, concentrations of chloroquine in the plasma tend to be higher than with other 4 aminoquinolines. Under accepted regimens of therapy employing loading doses, effective chloroquine concentrations are reached within from two to three hours. When the drug is given intramuscularly, therapeutically effective plasma chloroquine concentrations are reached in less than 15 minutes.

FIG 5 INDIVIDUAL CONCENTRATIONS AND GROUP MEANS OF CHLOROQUINE IN PLASMA DURING AND FOLLOWING 6-DAY THERAPEUTIC COURSES *



X = end of treatment

— mean concentration

..... individual concentration

* 200 mg of chloroquine (base) 4 times daily the first day followed by 100 mg of chloroquine (base) 4 times daily for 5 days

After Coatney et al¹¹

Dosage and route of administration
See chapter 5

Test for estimation in body fluids

A double extraction procedure for the estimation of chloroquine in body fluids has been worked out by Brodie et al ²⁴

Reagents

(a) Standard solution of chloroquine, 100 mg per litre 161 mg of the diphosphate salt are dissolved in 1 litre of 0.1 N HCl. This solution is stable when stored in the refrigerator. Working standards are prepared daily by dilution with 0.1 N HCl

(b) 0.1 N NaOH

(c) Heptane a technical grade of heptane is purified by successive washings with 1 N NaOH, 1 N HCl, and water

(d) Absolute ethanol

(e) 0.1 N HCl

(f) 0.5 N NaOH 1 ml should be neutralized by 5 ml of the above 0.1 N HCl

(g) Buffer reagent, pH 9.5 5 volumes of 0.6 M boric acid in 0.6 M KCl are added to 3.2 volumes of 0.6 N NaOH. When diluted as described in the procedure and after the addition of the cysteine reagent, the resulting pH should be 9.4-9.6. This pH should be checked by direct measurement

(h) 5% cysteine reagent 1000 mg of cysteine hydrochloride is dissolved in 20 ml of water. This solution is neutralized by the addition of 0.8 ml of 10 N NaOH. This reagent should be made fresh daily and neutralized just before use

Procedure

(a) Add 1-10 ml of biological sample (containing up to 1 µg of chloroquine) and an equal volume of 0.1 N NaOH to 30 ml heptane in a 60-ml glass stoppered bottle

(b) Shake for 30 minutes. Allow the phases to separate, centrifuging if necessary

(c) Add 8 drops of ethanol and mix with the heptane phase so as not to disturb the aqueous phase

(d) Transfer the heptane to a 125-ml glass stoppered bottle, add about twice the volume of 0.1 N NaOH and shake for 5 minutes

(e) After settling add 8 drops of ethanol to the heptane and mix as before. Remove the aqueous phase by aspiration

(f) Repeat the washing with 0.1 N NaOH, add 5 drops of ethanol, and transfer 20 ml of the heptane to a 60-ml glass stoppered bottle containing 6 ml of 0.1 N HCl

(g) Shake for 3 minutes and then centrifuge for 2 minutes

(h) Transfer 5 ml of the acid phase to a fluorometer tube containing 1.0 ml of 0.5 N NaOH and 1.5 ml of buffer reagent. Add 0.5 ml of cysteine reagent and mix

(i) A reagent blank, with water substituted for plasma or urine, is run through the same procedure

Standards are prepared by adding known amounts of the drug in 5 ml of 0.1 N HCl to 1 ml of 0.5 N NaOH and 1.5 ml of buffer in fluorometer tubes. 0.5 ml of cysteine reagent is added to each tube. A "dummy", consisting of acid, alkali, buffer, and cysteine reagent, is used for the blank setting of the fluorometer. After 30 minutes all tubes are irradiated with ultra-violet light, as described below

The intensity of fluorescence of the irradiated samples is determined in the Coleman photofluorometer, using Coleman B₁S and Coleman PC₁ filters. The sensitivity of the instrument is set by quinine, since the irradiated standards may slowly lose their fluorescence on frequent exposure to the ultra-violet light of the fluorometer

Irradiation of the 4-aminoquinolines is effected in a simply constructed irradiator, using an H-4 mercury arc lamp as the light source. The samples are placed in a circular rack surrounding the lamp so that they are equidistant from the lamp, and are irradiated for 3 hours. A fan is used for keeping the temperature of the solutions below 35°C during irradiation

Salts in common use

Chloroquine diphosphate and dihydrochloride, amodiaquine dihydrochloride dihydrate

Physical data regarding salts

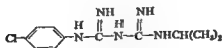
See Annex 3

Synonyms

See Annex 4

Proguanil *

Formula



proguanil N₁-p-(chlorophenyl) N₆-isopropyl biguanide

* See Selected bibliography, No. 89 113 (page 110)

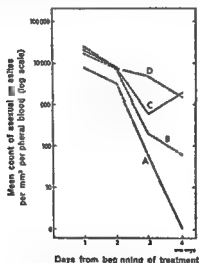
Activity in human malaria

(a) Sporozoites Probably inactive

(b) Primary exoerythrocytic forms Proguanil is highly active against the primary exoerythrocytic forms of *P. falciparum* and has a fleeting inhibitory action on those of *P. vivax*, its action on the presumed primary exoerythrocytic forms of *P. malariae* is unknown. It is thus a powerful drug for *causal prophylaxis* in *falciparum malaria*.

(c) Asexual blood forms Active against the asexual blood forms of all species of human malaria parasite. It will achieve *clinical cure* in all forms of malaria, with *radical cure* in most *falciparum* infections, but the clinical response is slow, and its use for the treatment of an acute malarial attack is not recommended. It is a good *suppressive* of all forms of malaria, often with *suppressive cure* in *falciparum* infection. It appears to act by inhibiting nuclear division.

FIG 6 PARASITAEMIA IN 258 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL ILLUSTRATING A DEVELOPING RESISTANCE IN THE SCHIZOGONIC BLOOD FORMS



A =	proguanil	single dose	100 mg (1947-8)
B =	"	"	250 mg or 300 mg (1948)
C =	"	"	250 mg or 300 mg (1948)
D =	"	daily	300 mg (standard course) (1950-1)
total			

CASES
25
40
74
119
258

Data from Malaria Research Division, Institute for Medical Research, Federation of Malaya, 1946-7

(f) Repeat the washing with 0.1 N NaOH, add 5 drops of ethanol, and transfer 20 ml of the heptane to a 60-ml glass-stoppered bottle containing 6 ml of 0.1 N HCl

(g) Shake for 3 minutes and then centrifuge for 2 minutes

(h) Transfer 5 ml of the acid phase to a fluorometer tube containing 1.0 ml of 0.5 N NaOH and 1.5 ml of buffer reagent. Add 0.5 ml of cysteine reagent and mix

(i) A reagent blank, with water substituted for plasma or urine, is run through the same procedure

Standards are prepared by adding known amounts of the drug in 5 ml of 0.1 N HCl to 1 ml of 0.5 N NaOH and 1.5 ml of buffer in fluorometer tubes. 0.5 ml of cysteine reagent is added to each tube. A "dummy", consisting of acid, alkali, buffer, and cysteine reagent, is used for the blank setting of the fluorometer. After 30 minutes all tubes are irradiated with ultra-violet light, as described below

The intensity of fluorescence of the irradiated samples is determined in the Coleman photofluorometer, using Coleman B₁S and Coleman PC₁ filters. The sensitivity of the instrument is set by quinine, since the irradiated standards may slowly lose their fluorescence on frequent exposure to the ultra-violet light of the fluorometer

Irradiation of the 4 aminoquinolines is effected in a simply constructed irradiator, using an H-4 mercury arc-lamp as the light source. The samples are placed in a circular rack surrounding the lamp so that they are equidistant from the lamp, and are irradiated for 3 hours. A fan is used for keeping the temperature of the solutions below 35°C during irradiation

Salts in common use

Chloroquine diphosphate and dihydrochloride, amodiaquine dihydrochloride dihydrate

Physical data regarding salts

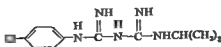
See Annex 3

Synonyms

See Annex 4

Proguanil *

Formula



proguanil N₁-P-(chlorophenyl)-N₂-isopropyl biguanide

* See Selected bibliography No. 89 113 (page 110)

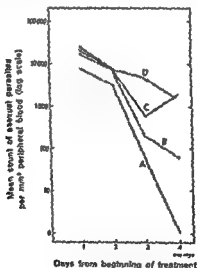
Activity in human malaria

(a) Sporozoites Probably inactive

(b) Primary exoerythrocytic forms Proguanil is highly active against the primary exoerythrocytic forms of *P. falciparum* and has a fleeting inhibitory action on those of *P. vivax*, its action on the presumed primary exoerythrocytic forms of *P. malariae* is unknown. It is thus a powerful drug for causal prophylaxis in falciparum malaria.

(c) Asexual blood forms Active against the asexual blood forms of all species of human malaria parasite. It will achieve clinical cure in all forms of malaria, with radical cure in most falciparum infections, but the clinical response is slow, and its use for the treatment of an acute malarial attack is not recommended. It is a good suppressive of all forms of malaria, often with suppressive cure in falciparum infection. It appears to act by inhibiting nuclear division.

FIG. 8. PARASITAEMIA IN 200 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL ILLUSTRATING A DEVELOPING RESISTANCE IN THE SCHIZOGONIC BLOOD FORMS

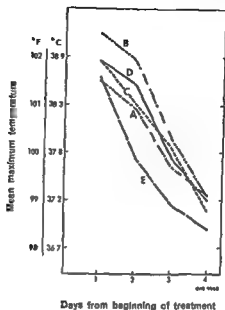


A =	proguanil	single dose	100 mg (1947-8)
B =	"	"	250 mg or 300 mg (1948)
C =	"	"	250 mg or 300 mg (1949)
D =	"	daily	300 mg (standard course) (1950-1)
total			

Cases
26
40
74
128
<hr/> 268

Data from Malaria Research Division, Institute for Medical Research, Federation of Malaya, 1946-7

FIG. 7 FEVER IN 913 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL OR QUININE



A	28
B	40
C	74
D	128
E	645
total	913

Data from Malaya Research Division Institute for Medical Research Federation of Malaya 1946-7

(d) **Gametocytes** Proguanil has little apparent effect on the production, numbers, or morphology of the gametocytes of *P. falciparum*, but in appropriate doses the drug inhibits the later development of sporogonic forms in the mosquito. Mosquitos fed on gametocyte carriers receiving therapeutic doses of proguanil do not become infective—an inhibitory effect on sporogony which lasts for varying periods up to ten days after the last dose, depending on the total quantity administered. Sporogony in *P. vivax* is similarly affected. Proguanil is thus a valuable drug for *sporontocidal prophylaxis*.

(e) **Secondary exoerythrocytic forms** Probably inactive, and hence a poor drug for *radical or suppressive cure* in *vivax malaria*. Its effect on the presumed secondary exoerythrocytic forms of *P. malariae* is unknown.

(f) **General** The outstanding virtues of proguanil are its extremely low toxicity, wide range of action, and relatively low cost. It is highly active as a causal prophylactic in falciparum malaria, is a good general suppressive, has a marked inhibitory effect on the transmission of malaria by mosquitos, but is not sufficiently rapid in action for treatment of the acute attack in non immune subjects. Its greatest drawback, a tendency to provoke resistance, is discussed in chapter 4 (page 59).

Toxicity

At the therapeutic dosage the toxicity of proguanil is very low, abdominal discomfort, loss of appetite, vomiting, and diarrhoea may be caused by doses of the order of 1,000 mg daily, more rarely, haematuria may be produced by such gross over dosage.

Contraindications

No contraindications are known other than the presence in the area of strains resistant either to proguanil or pyrimethamine (see chapter 4, page 64).

Absorption, elimination, plasma concentration

Absorption is rapid, elimination is fairly slow, mainly in the urine, in which the drug may be detected for several days after the last dose. About 40% is excreted in the urine and faeces, some of the remainder is converted into an active metabolite. Peak concentrations in plasma are attained about four hours after oral administration. The concentration in the red cells is from four to eight times greater than in the plasma. Plasma levels fall below the level of accurate estimation within a week, even after heavy and prolonged dosage.

Dosage and route of administration

See chapter 5

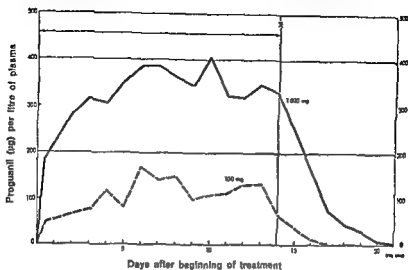
Test for estimation in body fluids

A simple test for proguanil in the urine has been devised by Gage & Rose⁷⁹

Reagents

(a) Copper sulfate analytical reagent (AR), 500 mg, and ammonium chloride AR, 1,330 mg, in 100 ml of distilled water

FIG 3 CONCENTRATION OF PROGUANIL (GROUP MEANS) IN PLASMA DURING ORAL TREATMENT WITH 100 mg AND 1,000 mg DAILY



X = end of treatment

After Adams et al.²⁰

(b) Sodium diethyldithiocarbamate 0.1% aqueous solution (the solution does not keep for more than a fortnight)

(c) 1 N NaOH

(d) Benzene the commercial grade redistilled is satisfactory

Procedure

(a) Mix 2 ml of urine, 1 ml of copper reagent, and 1 ml of the caustic soda solution in a stoppered tube and allow to stand for a few minutes

(b) Add 5 ml of benzene and shake for 2 minutes. Decant or pipette off the benzene into a second tube, wash with 1 ml of water, and transfer to a third tube

(c) Shake with 1 ml of sodium diethyldithiocarbamate solution for 1 minute

The intensity of the golden yellow colour is a measure of the amount of proguanil

Salts in common use

Monohydrochloride, acetate, lactate

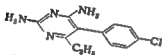
Physical data regarding salts
See Annex 3

Synonyms

See Annex 4

Formula

Pyrimethamine *



pyrimethamine 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine

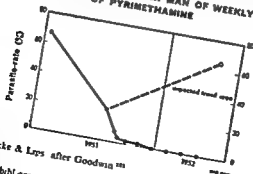
Activity in human malaria

(a) Sporozoites Probably inactive

(b) Primary erythrocytic forms It is thought that pyrimethamine may have some effect against these forms, but the degree of such action has not yet been defined

(c) Asexual blood forms Active against these forms in all types of malaria, producing clinical cure in all and radical cure in most cases of *P. falciparum* infection. Its action is, however, slow, and it is therefore not recommended for treatment of the acute attack. Dose for dose, pyrimethamine is the most powerful suppressive agent known. suppressive cure is achieved against *P. falciparum* infection and sometimes against *P. vivax*. Like proguanil it appears to act by inhibiting nuclear division.

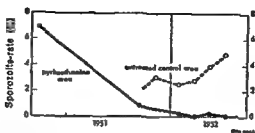
FIG 9 EFFECT ON PARASITE RATE IN MAN OF WEEKLY 25-mg DOSES OF PYRIMETHAMINE



Data from Vincke & Laps after Goodwin

* See Selected bibliography No 114-130 (page 111)

FIG 10 EFFECT ON SPOROZOITE RATE IN MOSQUITOS OF WEEKLY 25-mg DOSES OF PYRIMETHAMINE



Data from Vincke & Lips after Goodwin ¹²¹

(d) **Gametocytes** There is no apparent effect on the production, number, or morphology of gametocytes, but the action of the drug inhibits subsequent sporogony in the mosquito, resulting in *sporontocidal prophylaxis*

(e) **Secondary exoerythrocytic forms** Active against certain strains of *P. vivax*, although the exact conditions necessary for such action, in dosage and time, are not clearly defined. Its effect against similar presumed stages of *P. malariae* is unknown.

(f) **General** Pyrimethamine is a potent drug of extraordinary effectiveness against erythrocytic parasites. Its chief characteristics are (1) small weekly doses can effect complete *suppression* of quartan malaria and *suppressive cure* of vivax and falciparum malaria, (2) by inhibiting sporogony it prevents transmission of malaria by mosquitos, (3) it is tasteless and therefore easy to administer to children, (4) it is relatively inexpensive. Its limitations are (i) that its action is too slow to warrant its use for treatment of an acute malarial attack in a non immune subject, (ii) drug-resistance may develop in the field, if it is administered in insufficient dosage (see chapter 4)

Toxicity

At the recommended dosage toxicity is very low, long term administration of 25 mg daily may result in a megaloblastic type of anaemia, but remission is rapid when the drug is discontinued.

Contraindications

No contraindications are known other than the presence in the area of strains resistant either to pyrimethamine or to proguanil (see chapter 4, page 64)

Absorption, elimination, plasma concentration

Studies in rhesus monkeys utilizing doses above those recommended for man have led to the following conclusions. Absorption of pyrimethamine from the intestinal tract is relatively slow but essentially complete. It is localized to a moderate degree in the lung, liver, kidney, and spleen. About 20% of the drug administered can be recovered in the urine, this represents metabolic products and unchanged drug. The drug does not ordinarily accumulate in the plasma. Peak concentrations following oral administration are reached in approximately two hours.

Dosage and route of administration

See chapter 5

Test for estimation in body fluids

At recommended dosages, plasma levels are too low for accurate determination, details of the test, therefore, are not included here. Those interested in the methyl orange test, modified for determining pyrimethamine concentration in body fluids, are referred to Schmidt, Hughes & Schmidt 122

Salts in common use

Pyrimethamine is prescribed as base, not as a salt

Synonyms

See Annex 4

CHAPTER 4

DRUG-RESISTANCE IN MALARIA *

One of the limiting hazards in the progress of chemotherapy is the parasite's flexible response to the drug. The parasite, be it virus, bacterium, protozoon, or metazoon, must adapt or perish. The drug in the host tissues may impose on the parasite metabolic demands which are beyond its capacity for individual or group adaptation: the parasite is then "drug-sensitive" and will remain sensitive. The parasite, on the other hand, may adapt itself to the new chemical environment, and to the extent of its successful adaptation it will become "drug-resistant."

Drug resistance from the adaptation of living organisms to substances which normally destroy them or prevent their growth has been known for many years. Kossiakoff,¹⁵² in 1887, showed that bacteria could be "trained" to grow in media containing antiseptics, and two years later Massart¹⁵³ proved that flagellates could be adapted to resist concentrations of sodium chloride normally toxic. Renewed interest in this interesting phenomenon was aroused with the discovery by Ehrlich, in 1908, that trypanosomes exposed to sublethal doses of trypanosomocidal drugs become resistant, and the later studies of Warrington Yorke and his colleagues brought the problem of drug-resistant trypanosomiasis to a sharp focus, but the wider implications of this work were not fully realized, and only with the discovery of acquired bacterial resistance to the sulfonamides, penicillin, and streptomycin, has drug-resistance made any serious impact on treatment. Today, it seems, drug-resistance may be the rising price that has to be paid for the quickening tempo of chemotherapeutic advance.

Significant drug-resistance in malaria is a recent phenomenon. No important antimalarial drug used before the end of the second World War was known to induce serious resistance. Quinine, pamaquine, and mepacrine, the mainstays of malaria therapy, had never given serious cause for anxiety on this score, and it seemed that the malaria parasite might lack the capacity for adaptation which certain bacteria were then beginning to show towards the sulfonamides and penicillin. But the discovery, in 1947, of acquired resistance to proguanil in the avian parasite *P. gallinaceum*

* See Selected bibliography, No 131-173 (page 114)

sounded a note of warning.^{122 168} The asexual blood forms of this species could be "trained"—if we may use the word "trained" with no implication of the mechanism involved—to resist high doses, and the resistance was stable enough to survive passage through mosquitos. In quick succession other species of *Plasmodium*, including *P. falciparum* and *P. vivax* infecting man, were shown to share this capacity for adaptation to proguanil, and for the first time drug resistance in malaria appeared as a significant clinical problem.

Definitions

The expression "drug resistant malaria" has a deceptive simplicity. Malaria parasites may be said to "resist" when exposure to a drug in the tissues of the host leaves at least some of them unharmed. They resist small doses of quinine and they resist many drugs which are lethal to other minute forms of life but have no interest as remedies for malaria. Resistance in this wide sense has little relevance to the clinical problems of drug resistant malaria, and in this discussion we shall consider it only in relation to drugs which, administered to the vertebrate host in adequate and safe doses, normally destroy or contribute to the destruction of malaria parasites at some stage or other in their life-cycle.

Resistance within the limits of dosage tolerated safely by the host may be absolute, or it may be relative to a normal sensitivity. Sporozoites are completely refractory to the largest doses of quinine the host will stand, within this limit their resistance is absolute. Resistance in particular geographical strains, on the other hand, is relative to the general sensitivity of other strains, and acquired resistance is relative to the initial sensitivity of the species before there has been significant drug contact.

Resistance to a drug is conveniently expressed in terms of the dosage administered with safety to the host. If, for example, the lowest lethal concentration for a parasite is attained on first exposure by a host dosage of 5 mg, but later only by 500 mg, the parasite is said to have acquired a hundredfold resistance. An arbitrary limit to resistance is reached when the dose which is lethal to the parasite is no longer safe for the host.

Natural resistance within a species

All malaria remedies are selective in their action. The parasite is not uniformly sensitive to drugs throughout its life-cycle, and at particular stages it may show a high degree of natural resistance. Sporozoites, possibly from their fleeting exposure in the human host, seem to resist all known drugs, and to most drugs the tissue forms are equally refractory. With few exceptions, the asexual blood forms in all species are sensitive

to all the accepted malaria remedies, while the gametocytes show marked specific differences in this respect. Table I illustrates this natural resistance within a species.

TABLE I. NATURAL DRUG RESISTANCE AT VARIOUS STAGES IN THE LIFE CYCLE OF *P. falciparum* AND *P. vivax*

	<i>P. falciparum</i>				<i>P. vivax</i>			
	sporozoites	tissue forms	blood forms (asexual)	gametocytes	sporozoites	tissue forms	blood forms (asexual)	gametocytes
Quinine	R	R	—	R	R	R	—	—
Mepacrine	R	R	—	R	R	R	—	—
Chloroquine	R	R	—	R	R	R	—	—
Pamaquine	R	—	R	—	R	—	—	—
Proguanil	R	—	—	—	R	R	—	—
Pyrimethamine	R	—	—	—	R	—	—	—

R = resistant

This selective resistance within a species is a fixed character in no way related to earlier exposure to a drug. It poses no novel problem and its acceptance has long been implicit in the planning of malaria therapy.

Resistance in geographical strains

Malarial infections from different parts of the world do not always respond equally well to the same treatment, and it seems that geographical strains of the same species of parasite sometimes differ in their sensitivity to particular drugs. The reason for these strain differences is not always clear. They may possibly express a natural variation related to geographical isolation, but the influence of previous contact with drugs can seldom be excluded.

Resistance acquired by previous drug contact

A high degree of drug resistance in a species normally sensitive is probably always an adaptive change related to previous exposure. A thousandfold resistance to proguanil has been produced experimentally in the blood forms of *P. vivax*¹⁴¹. Malayan strains of *P. falciparum*, sensitive in 1947 to a single dose of 100 mg of proguanil, were resistant to many times this dose two years later⁸⁸. The asexual blood cycle of the monkey

parasite, *P. cynomolgi*, is naturally sensitive to pyrimethamine, but highly-resistant strains may appear under laboratory conditions ¹²⁷

The range of drug-resistance

All forms of the malaria parasite normally sensitive to drugs may in theory become resistant. The problem of drug resistance must hence be considered in relation to the asexual tissue forms, to the asexual blood forms, and to the gametocytes, and even, by a carry-over effect on the gametocytes, to the sporogonic forms in the mosquito.

Resistance to the Common Antimalarial Drugs

Quinine

The parasites of human malaria are sensitive to quinine at important but restricted phases in their life-cycle. The schizogonic blood forms of all species infecting man are sensitive, and so are the gametocytes of *P. vivax*, *P. ovale*, and *P. malariae*.

A lessened sensitivity to quinine in the asexual blood forms of *P. falciparum*, presumed to be natural, has been reported from several parts of the world. An Italian strain of *P. falciparum* has been shown to be much less sensitive to quinine than an Indian strain observed under the same conditions, ¹²⁸ and a Panamanian strain is reported to have shown a mild relative resistance, ¹²⁹ the New Guinea Chesson strain of *P. vivax* seems to be less sensitive than the McCoy strain indigenous in the United States of America. ²⁷ The "quinine resistant" malaria reported from Mesopotamia after the first World War may possibly have some such explanation, but quinine-resistance was then held to explain a poor clinical response for which there were other possible causes.

Acquired resistance to quinine in human malaria is rare, if indeed it occurs at all. Certain writers refer to a "dulling of the quinine effect", observed during the first World War, but little support for this view has appeared since, and Fletcher, ¹³⁰ with this wartime experience in mind, found that quinine-resistance in cases observed in Malaya vanished when he gave the drug with his own hands. In avian malaria, experimental attempts to induce resistance by intensive quinine treatment have either failed ¹³¹⁻¹³⁵ or have achieved no more than a slight resistance. ¹³⁶ A trifling cross-resistance between pamaquine and quinine has been reported ¹³⁷

Pamaquine

Prolonged exposure to pamaquine may induce a slight resistance in the asexual erythrocytic forms of certain avian and mammalian species of

Plasmodium,^{133 139 143 144 156} but acquired resistance in species infecting man has not been reported. The asexual blood forms of *P. falciparum* have a marked natural resistance to pamaquine. Pentaquine, isopentaquine, and primaquine, 8 aminoquinolines related to pamaquine, are presumed to have similar tendencies. Pamaquine resistance in *P. gallinaceum* confers no resistance to mepacrine, chloroquine, or proguanil, but pamaquine-resistant strains may be slightly resistant also to pentaquine and quinine.¹³⁹

Mepacrine

Experimental attempts to induce resistance to mepacrine in avian and mammalian species have failed,^{133 139 160 168 169} and the risk of acquired mepacrine-resistance in human malaria seems to be small. There is an isolated report, however, of a relative resistance to mepacrine in strains of *P. falciparum* observed in the Aitape-Wewak area of New Guinea. These resisting strains regularly produced overt malaria in volunteers receiving 100 mg of mepacrine daily, a suppressive dosage which was efficient elsewhere in New Guinea and, indeed, in other parts of the world. This resistance seems to have been acquired, for the resisting strains were isolated from a selected group of patients repeatedly given a standard quinine-mepacrine pamaquine treatment for recrudescant attacks. Under the same conditions there was no evidence of resistance in *P. vivax*.⁸⁹

Chloroquine

Like mepacrine, this drug has little tendency to induce resistance in malaria parasites exposed to its action. Experimental attempts to induce resistance in the avian parasites *P. gallinaceum* and *P. lophurae*, in the monkey parasite *P. cynomolgi*, and in *P. vivax* of man, have been unsuccessful.^{138 141 161 168}

Amodiaquine

Resistance to amodiaquine has not been reported and on chemical and pharmacological grounds any tendency in this direction seems improbable. An attempt to induce resistance in *P. lophurae* (chicks) was not successful.¹⁶⁶

Pyrimethamine

Experience of pyrimethamine in the treatment and prevention of human malaria is still limited, and comparatively little is known of resistance to this drug in the species infecting man. Resisting strains have been produced experimentally in *P. cynomolgi*,^{127 168} *P. knowlesi*,^{123b} and *P. vivax*.¹²³

A mild resistance in *P. falciparum* has been reported from an area in Malaya where proguanil resistance is well established,¹⁷⁰ and Jones, experimenting on himself, has proved that a proguanil-resistant *falciparum* strain from this area was resistant also to pyrimethamine.¹⁴⁹ Experience in Kenya shows how quickly resistance in this species may appear and spread after mass treatments.¹⁵⁰

Proguanil-Resistance

As noted earlier, the tendency of proguanil to produce resistance has considerably modified early optimism and its place in the future patterns of therapy is now less certain. The problem of proguanil resistance has been very extensively studied since it was first reported in 1947.

In the laboratory a resistance to proguanil appears when parasites are exposed to significant but sublethal doses of the drug, usually with repeated blood passage from host to host, conditions which are exceptionally favourable for the emergence of resistant strains. From later work, however, it seems that a resistance in *P. falciparum*, *P. vivax*, and *P. malariae* may appear under the less favourable circumstances of field and hospital practice.

Range

Resistance to proguanil may occur, theoretically, at any or all of the three stages in the life-history of the parasite on which it acts.

1 *Exoerythrocytic forms* The exoerythrocytic forms of *P. vivax*, and probably those of *P. malariae* and *P. ovale*, are naturally resistant to proguanil, but the pre-erythrocytic forms of *P. falciparum* in the tissues are highly sensitive. It seems, however, that this sensitivity may be lessened in *falciparum* strains with established resistance in the erythrocytic cycle. Primary *falciparum* infections have been acquired by newcomers to Malaya naturally exposed to resistant strains and alleged to have taken 100 mg of proguanil daily for weeks or months beforehand, moreover, a human volunteer, bitten by mosquitos infected from a resistant Malayan strain, developed overt *falciparum* malaria 11 days later despite regular daily doses of 100 mg of proguanil during the incubation period.¹⁴⁷ Resistance has also been reported in the pre-erythrocytic forms of the monkey parasite, *P. cynomolgi*,¹⁴⁷ and of the avian parasite, *P. gallinaceum*.¹⁴⁸

2 *Asexual blood forms* Acquired resistance to proguanil in the asexual blood forms has been reported not only in avian species of *Plasmodium*, but in three of the species infecting man (table II). Prolonged contact with proguanil under appropriate experimental conditions may induce a resistance so high that the tolerance of the parasite for the drug may become

greater than that of the host.¹⁴² Resistance has also been encountered in the course of clinical or preventive practice in malarious countries, though the recorded incidence is low; moreover, the resistance has been slow to develop and moderate in degree.^{98 112 140a 140b 144a}

TABLE II PROGUANIL-RESISTANCE IN THE ASEQUAL BLOOD FORMS OF VARIOUS SPECIES OF *PLASMODIUM*

Species	Strain No	How acquired	Months to acquire	Degree	Transmission through mosquitos
<i>P. gallinaceum</i> (chick)	132	experimental	5	high	yes
"	168	"	"	moderate	yes
<i>P. lophurae</i> (duck)	168	"	7	moderate	
<i>P. cynomolgi</i> (monkey)	146	"	14	high	
"	160	"	"	high	yes
"	147	"	16	high	yes
<i>P. falciparum</i> (man)	131, 162	"	10	high	yes
"	98	field conditions	24	moderate	
"	140b	natural			
<i>P. vivax</i> (man)	163	experimental	20	high	yes
"	141	"	4-6	high	
"	171	field conditions	48	moderate	
<i>P. malariae</i> (man)	100	"		moderate	

3 *Gametocytes* Resistance to proguanil, once established in the erythrocytic cycle, may extend to the gametocytes. The experimental evidence on this point is scanty, but decisive. Mosquitos have been infected with a proguanil resistant strain of *P. gallinaceum* while the host chicks were receiving full doses of the drug,¹³³ and a resistant strain of *P. falciparum* from a gametocyte carrier receiving 100 mg of proguanil daily has

Rate of development

Resistance to proguanil may appear quickly, or slowly, or indeed not at all. Under artificial conditions, the rate of development of resistance is calculated to favour the survival of resisting organisms, a high tolerance to proguanil in the asexual blood forms of *P. falciparum* and *P. vivax* may appear within a few months.

The usual conditions of clinical or preventive practice in malarious countries are never so favourable for the production of resistance as are those of the laboratory, they are seldom likely to be decisively unfavourable. The possible trend of events in malarious regions where proguanil is used freely may be illustrated by experience in Malaya. Here the drug was first used for treatment and prevention early in 1947, and records of the proguanil response in acute infections contracted in a single district have been kept for nearly six years. At first, a single dose of 100 mg of proguanil would terminate acute falciparum attacks. The first recorded failure of single dose therapy was in October 1948 and the first failure of a standard therapeutic course (300 mg \times 7) in April 1949. By 1950, nearly half of the falciparum infections treated failed to respond to a full therapeutic course. In *P. vivax*, a definite proguanil resistance was proved only in January 1951, and its incidence has remained low. Resistance in *P. malariae* has not yet been recognized in Malaya but has been reported from Indonesia.¹⁰⁰

Proguanil suppression in Malaya, started experimentally in December 1946, has since been used as a standard method of control on many rubber estates and by the Security Forces. There was good evidence that a 100-mg dose twice a week was very efficient in the early days. Five years later, in certain districts there were indications that a daily suppressive dose of 100 mg would sometimes fail, though by and large the drug was still thought to be a very useful suppressive.

Stability

Once established, proguanil resistance in the asexual blood forms appears to be fairly stable. It may persist through many asexual generations, and it may be unchanged by a transfer of the parasite to a fresh host whether by blood or mosquito-passage. Resistance in *P. gallinaceum* has been shown to last for at least a year without further exposure to the drug,¹²¹ and to survive serial passage through mosquitos,¹²² while there is suggestive evidence that resistance in *P. knowlesi* may persist for at least eight months.¹²³ Resistant strains of *P. cynomolgi*, *P. falciparum*, and *P. vivax* have been shown to remain resistant after mosquito transmission to a fresh host.^{127 120 122 123}

Spread under field conditions

In latent infections, with few parasites in the peripheral blood, attempts to induce resistance have been unsuccessful.^{124 125} It may thus be assumed that the primary factors in causation are under-dosage and significant parasitaemia, operating together, and, under field conditions, found particularly in the under treated acute attack and in the under suppressed

greater than that of the host.¹⁴¹ Resistance has also been encountered in the course of clinical or preventive practice in malarious countries, though the recorded incidence is low, moreover the resistance has been slow to develop and moderate in degree.^{98 113 140a 140b 144a}

TABLE II PROGUANIL RESISTANCE IN THE ASEYUAL BLOOD FORMS OF VARIOUS SPECIES OF PLASMODIUM

Species	Bib No	How acquired	Months to acquire	Degree	Transmission through mosquitoes
<i>P. gallinaceum</i> (chick)	132 168	experimental	5	high moderate	yes yes
<i>P. lophurae</i> (duck)	166		7	moderate	
<i>P. cynomolgi</i> (monkey)	146 180 147		14 16	high high high	yes yes
<i>P. falciparum</i> (man)	131 162 98 140b	field conditions natural	10 24	high moderate	yes
<i>P. vivax</i> (man)	163 141 171	experimental field conditions	20 4-6 48	high high moderate	yes
<i>P. malariae</i> (man)	100			moderate	

3 *Gametocytes* Resistance to proguanil, once established in the erythrocytic cycle, may extend to the gametocytes. The experimental evidence on this point is scanty, but decisive. Mosquitos have been infected with a proguanil resistant strain of *P. gallinaceum* while the host chicks were receiving full doses of the drug,¹³³ and a resistant strain of *P. falciparum* from a gametocyte carrier receiving 100 mg of proguanil daily has

Rate of development

Resistance to proguanil may appear quickly, or slowly, or indeed not at all, depending on the conditions of exposure to the drug. Under artificial conditions, with deliberate under dosage, with careful timing of treatment, and with a serial transfer of parasites to fresh hosts calculated to favour the survival of resisting organisms, a high tolerance to proguanil in the asexual blood forms of *P. falciparum* and *P. vivax* may appear within a few months.

The usual conditions of clinical or preventive practice in malarious countries are never so favourable for the production of resistance as are those of the laboratory, they are seldom likely to be decisively unfavourable. The possible trend of events in malarious regions where proguanil is used freely may be illustrated by experience in Malaya. Here the drug was first used for treatment and prevention early in 1947, and records of the proguanil response in acute infections contracted in a single district have been kept for nearly six years. At first, a single dose of 100 mg of proguanil would terminate acute falciparum attacks. The first recorded failure of single-dose therapy was in October 1948 and the first failure of a standard therapeutic course (300 mg \times 7) in April 1949. By 1950, nearly half of the falciparum infections treated failed to respond to a full therapeutic course. In *P. vivax*, a definite proguanil resistance was proved only in January 1951, and its incidence has remained low. Resistance in *P. malariae* has not yet been recognized in Malaya but has been reported from Indonesia.¹⁰⁰

Proguanil suppression in Malaya, started experimentally in December 1946, has since been used as a standard method of control on many rubber estates and by the Security Forces. There was good evidence that a 100-mg dose twice a week was very efficient in the early days. Five years later, in certain districts there were indications that a daily suppressive dose of 100 mg would sometimes fail, though by and large the drug was still thought to be a very useful suppressive.

Stability

Once established, proguanil resistance in the asexual blood forms appears to be fairly stable. It may persist through many asexual generations, and it may be unchanged by a transfer of the parasite to a fresh host whether by blood or mosquito-passage. Resistance in *P. gallinaceum* has been shown to last for at least a year without further exposure to the drug,¹²⁴ and to survive serial passage through mosquitos,¹²⁵ while there is suggestive evidence that resistance in *P. knowlesi* may persist for at least eight months.^{125a} Resistant strains of *P. cynomolgi*, *P. falciparum*, and *P. vivax* have been shown to remain resistant after mosquito transmission to a fresh host.^{127 128 129 132}

Spread under field conditions

In latent infections, with few parasites in the peripheral blood, attempts to induce resistance have been unsuccessful.^{124 126} It may thus be assumed that the primary factors in causation are under-dosage and significant parasitaemia, operating together, and, under field conditions, found particularly in the under treated acute attack and in the under suppressed

smouldering infection. The most fertile source of resistant parasites is likely to be the under-treated attack in which a parasite population of the order of 10^9 - 10^{11} or more is exposed to a dose of drug sufficient only to destroy the more sensitive members.

Suppressive proguanil-therapy is likely on theoretical grounds to pose a lesser problem of resistance, for parasitaemia in the under suppressed infection will usually be low. But here again under-dosage from irregular administration will greatly raise the odds. With missed doses, parasitaemia may rise to a clinical level and the dual effect of a high concentration of parasites and a low concentration of drug come into play.

Resistance developing from under-dosage is at first a personal problem, restricted to the subjects whose parasites have become proguanil tolerant. In time the resisting parasites would die out were they not transferred to a new host. Resistance becomes a community problem when the resisting strains are diffused by mosquitos. The extent of spread is determined by

parasites in mosquitos, the transmission of resisting strains, no less than their initiation, is likely to be related to under dosage.

Recognition

Proguanil resistance may declare itself in various ways

(a) The failure of a single dose to achieve in mild acute infections a remission of symptoms and to eliminate the schizogonic cycle in the blood is evidence of a slight loss of sensitivity. This was the earliest indication of a developing resistance in Malayan strains of *P. falciparum*. Today, however, routine single dose proguanil therapy is not recommended and this method of detecting early resistance has no more than experimental interest. The failure of a standard therapeutic course of 300 mg daily in acute infections to clear asexual parasites from the blood within seven days indicates a growing resistance in the schizogonic blood forms, but again this method of assessing resistance will usually be experimental, for proguanil alone is seldom recommended today for the treatment of the acute attack.

(b) The occurrence of overt malaria in inhabitants of endemic areas who are known to have taken regular suppressive doses of proguanil may suggest that resistance is developing, although perhaps only in the asexual blood forms of the parasite.

(c) The occurrence of overt malaria in newcomers who have taken 100 mg proguanil daily without fail since arrival in the malarious area suggests the transmission of parasite strains which are resistant to proguanil.

at various stages of their life-cycle. The first suspicion of resistance in the pre erythrocytic forms of certain Malayan strains of *P. falciparum* arose in this way. The difficulty is that one can seldom be certain that the proguanil has been taken with unfailing regularity.

(d) Resistance at the sporogonic stage cannot be assessed by simple clinical means. The conditions of transmission in most malarious countries are too complex, and the only valid evidence is likely to be that which comes from mosquitos infected experimentally in the laboratory.

Prevention

Proguanil resistant parasites are not likely to arise in the individual subject if the schizogonic cycle in the blood is permanently interrupted by efficient treatment or inhibited by efficient suppression. They cannot be transmitted and spread in the community if the continued development of the gametocytes is inhibited by adequate therapy, clinical or suppressive, for every infected person. In most malarious countries this is possibly a counsel of perfection. The occasional resisting strain is likely to emerge in any community using proguanil on a large scale and lacking a high level of medical organization. Whether the resisting strains are few or many, whether they die out or spread, must finally be determined by the prevailing standards of treatment, suppression, and mosquito control. Treatment must be good enough to eliminate asexual parasites from the blood, and continued long enough to sterilize gametocytes. Suppression must be regular enough to prevent the transient bursts of parasitaemia which may come with missed doses.

The fact that resistance to proguanil is most likely to arise when a large parasite population is exposed to, but not eliminated by, the drug is in itself a sufficient reason why acute infections should not be treated with proguanil alone. When the drug is used for malaria suppression, resistance is likely to arise only when the plasma concentration falls low enough to permit an active proliferation of parasites. Irregular dosage is likely to be the common cause, and the key to prevention probably lies in a good suppressive discipline. For a time the loss of effect from early resistance can be met by an increase in dosage—this is apparently the situation in parts of West Africa—but a further rise or spread of resistance would necessitate an immediate change of drug.

It is not always easy to arrive at a decision when resistance is mild or sporadic, and when proguanil, though still a useful suppressive, sometimes fails. What margin of failure is to be considered tolerable in the light of the other virtues of the drug? To what extent should we weigh in the balance the great potential value of proguanil as a safe causal prophylactic in *falciparum* infection and as a non toxic sterilizing agent for mosquito

infections? This is a problem which faces public health authorities in some territories today, and there is no clear answer. We may take the view that the most efficient suppressive drug should always be the drug of choice—the 4-aminoquinolines and mepacrine are better suppressives than proguanil under the conditions prevailing, for example, in certain parts of Malaya. Or we may regard the direct action of proguanil on the pre-erythrocytic and sporogonic forms as a powerful asset not to be discarded lightly. A deciding factor might well be the proguanil sensitivity of the prevailing strains at the pre-erythrocytic and sporogonic phases of growth. Should this sensitivity be lost, there would be a strong indication for a change-over to another drug.

Cross-Resistance

The fear that a resistance to one drug might confer on malaria parasites a general tolerance to other antimalarial drugs has proved to be ill founded. Cross-resistance certainly occurs, sometimes to a marked degree, but the phenomenon presents no clinical problem which cannot be met simply by a change of drug. Experimental evidence suggests that the only important compounds to which malaria parasites may show a significant cross-resistance are proguanil, pyrimethamine, and the sulfonamides (table III).

Cross-resistance between proguanil and the sulfonamides has much theoretical interest, but the sulfonamides are not used as malaria remedies, and there is little danger of proguanil-resistant malaria from sulfonamide therapy in other diseases.

The extent and significance in human malaria of a cross resistance between proguanil and pyrimethamine has still to be assessed. Pro-

resistance in the local falciparum strains. Resistance to pyrimethamine in the Chesson strain of *P. vivax* confers a partial resistance to proguanil.¹²² This disturbing cross-resistance might well restrict the use of proguanil and pyrimethamine in territories where resistance to one of them is known to occur.

The three drugs, proguanil, pyrimethamine, and sulfadiazine, all seem to act on malaria parasites in much the same way—by inhibiting nuclear division. They all tend to induce a high resistance in parasites exposed to their action, and resistance in any one of them may extend to one or more of the others. Quinine, mepacrine, and the 4-aminoquinolines do not induce significant resistance nor are they involved in cross-resistance. They are chemically unrelated to proguanil, pyrimethamine, and the sulfon-

TABLE III CROSS RESISTANCE BETWEEN ANTIMALARIAL DRUGS

Species	Bib No	Primary acquired resistance	Associated resistance	Resistant strain still sensitive to
<i>P. gallinaceum</i>	134 136 137	sulfadiazine	proguanil other sulfonamides	quinine mepacrine pamaquine
"	168	proguanil	—	quinine mepacrine sulfadiazine
"	136 157	proguanil	sulfadiazine (slow)	
"	139	pamaquine	pentasquine quinine (slight)	proguanil mepacrine sulfadiazine chloroquine
<i>P. berghei</i>	48	sulfadiazine	proguanil (slight)	
"	48	proguanil	pyrimethamine (slight)	
<i>P. lophurae</i>	168	proguanil		pamaquine quinine mepacrine chloroquine amodiaquine
<i>P. cynomolgi</i>	147 160	proguanil		chloroquine mepacrine pentasquine sulfadiazine
"	127	pyrimethamine	proguanil	chloroquine
<i>P. knowlesi</i>	165	proguanil	pyrimethamine	
<i>P. falciparum</i>	125 140	proguanil	pyrimethamine	
<i>P. vivax</i>	141	proguanil		chloroquine
	122	pyrimethamine	proguanil	chloroquine

amides, and they probably act on malaria parasites by a different metabolic route. Schmidt and his colleagues have drawn attention to a possible parallel with the bacteriostatic sulfonamides and the bacteriocidal penicillins, and suggest that resistance in malaria parasites develops in relation to drugs which inhibit the growth of the parasites, rather than to drugs which destroy them.¹⁰⁰

Origin and Mechanism of Drug-Resistance

Drug resistance in human malaria may be explained in various ways. We may assume that the new chemical environment imposed by the drug induces a change in all the parasites enabling them to find a metabolic pathway of escape from its lethal effects, this is the theory of physiological adaptation. Or we may assume that resistant parasites arise by chance as

rare mutants and that the drug is merely a selective agent, this is the theory of spontaneous mutation. Or, again, we may accept mutation as the key to resistance, but assume that mutations are bound up in some way with exposure to the drug, this may be called the theory of induced mutation. Yet again, we may accept the simple theory advanced by Yudkin,¹⁷³ which assumes that cell division does not necessarily distribute the systems responsible for resistance equally between the daughter cells. Repeated divisions would produce a clone of cells with the average resistance of the parent cell, but with a distribution of greater or lesser resistance around that of the parent cell. The drug might then have the effect of destroying the cells of lesser resistance, with a progressive shift of the average towards a higher resistance, this is the theory of clonal variation with selection.

Physiological changes directly induced by environment involve potentially all members of an exposed population. They are thought to be non-inheritable and hence impermanent. Changes arising from mutation, on the other hand, involve the genetic or heredity producing mechanism of the cell and are passed on from generation to generation. They appear only in a minute proportion of cells, and tend to be stable and permanent, finding expression in the population as a whole by the selective influence of environment and they are liable to occur as a sudden event, or as a continuous "step wise" series of events, rather than as a gradual and continuing process. Clonal variation would similarly be expected to produce inheritable change, tending to permanence, but occurring rather as a smooth and continuing process.

The mechanism of drug resistance

The observed phenomena of drug resistance in malaria, while suggesting a genetic origin, give little clue to the mechanism of change. The character of resistance is carried throughout the life-cycle of the parasite in vertebrate and invertebrate hosts, it continues unchanged from generation to generation in the asexual blood forms, it tends to persist when the exciting stimulus has been withdrawn, and it is readily produced only in parasite populations large enough to include a few resistant members. An abrupt appearance of resistance has been reported but a rather gradual development seems to be more usual. These are phenomena for which spontaneous mutation, induced mutation, or clonal variation, could equally provide satisfying explanations, though it is perhaps significant that the drugs which give rise to serious resistance are those which apparently interfere with the division of nuclear chromatin. Beyond this general statement we cannot go, for genetic studies of malaria parasites are exceedingly difficult, and little work seems to have been done on this subject.

The nature of resistance

If there is little assurance as to the origin of resistance in malaria parasites, there is even less regarding the changes within the parasites which enable them to resist. The problem is bound up with the metabolism of the parasites and with the precise mode of action of drugs, and existing knowledge on these subjects is still fragmentary.

Drug resisting parasites are clearly different in some way from those which do not resist. The differences are not evident in their form, nor, in the absence of the drug, in their behaviour. They are subtler differences related to the metabolism of the parasite cell. We may conceive, for example, that the permeability of the parasite to certain drugs is subject to variation. Resistance might then arise by the selection of variant parasites which deny access to the interior of the cell. The resistance of trypanosomes to organic arsenicals has been explained in this way. Or variation might involve the enzymic constitution of the parasite cell, with resistance appearing where, for example, a variant parasite is able to dispense with an enzyme system normally subject to interference by the drug. If, as we may suppose, a drug acts by disturbing the synthesis or utilization of some essential metabolite, the parasites may conceivably evade this action (a) by an increased production of the metabolite, or (b) by finding an alternative pathway for its synthesis, or (c) by a capacity to grow in its absence. The sulfonamides appear to act on certain bacteria by competing with the metabolite *p*-aminobenzoic acid in an essential enzymic system, while an increased production of this metabolite is associated with sulfonamide-resistance. Can we relate this evidence to sulfonamide-resistance in malaria? Pteroylglutamic acid, a product of the metabolism of *p*-aminobenzoic acid, inhibits the action of sulfadiazine and proguanil in certain forms of malaria.¹⁴⁵ May we then presume that resistance to these drugs is related to parasite variations involving the synthesis of, or need for, pteroylglutamic acid? Evidence in this highly complex field is steadily accumulating, but whether, or to what extent, these or similar mechanisms come into play in drug resistant malaria is not yet clear.

Commentary

The main phenomena of drug resistance in malaria may be stated in a few words. At particular phases in their life-cycle, malaria parasites evolve a means of surviving in the presence of drugs which normally destroy them. The resistance seems to be causally related to the exposure, usually prolonged and intermittent, of large parasite populations to a near lethal dose of drug. The resistance is inheritable and fairly stable. It involves

mainly the schizogonic forms in the blood, but in some species it occurs also in the pre erythrocytic forms, and in the gametocytes. The drugs which excite resistance are those which appear to act by inhibiting nuclear division—proguanil, pyrimethamine, and the sulfonamides. Cross resistance between these drugs may occur. Drugs like quinine, mepacrine, chloroquine, and pamaquine—which appear to act in some other way—do not give rise to significant resistance.

The most satisfying theories assume that resistance is due to the selective survival of resisting organisms arising by mutation or by "clonal variation." Whether the resisting organisms appear at random or are changed in some way by the drug we do not know. Nor do we know in what way the parasites are changed. Do they resist the penetration of the drug, or does resistance depend on their enzymic constitution? Have the resistant parasites some other pathway for the synthesis of a necessary metabolite, the synthesis normally arrested by the drug? If so, is the same enzyme system involved at the three phases of the life-cycle in the tissues, the blood, and the mosquito's stomach? Having arisen at some point, does resistance extend throughout the cycle? Is resistance a permanent quality or will it die away in time when the exciting stimulus is withdrawn? These questions, and the doubts which they engender, emphasize the need for a better understanding of the intricate problems still awaiting solution.

CHAPTER 5

THE CLINICAL USE OF ANTIMALARIAL DRUGS*

Chemotherapy has scored some of its greatest successes in the treatment of human malaria. There are few infections more responsive to well-directed therapy, and fewer in which therapy can be applied with results so satisfying on so wide a front. The first, perhaps still the greatest, success came with the discovery three centuries ago that the bark of cinchona would "cure" certain fevers. The patient sick with the ague took the remedy, and was soon well again—the simplest and still the main clinical approach to malaria chemotherapy. But the fever often came back, and as early as the 17th century Sydenham had broadened this simple concept to embrace the idea of prevention. He gave the bark to persons who expected a recurrence of the fever but who were not sick at the time. After the isolation of the principal alkaloids of cinchona, the small daily dose of quinine came to be adopted as a clinical preventive.

The practice of using cinchona or quinine to end the malarial attack and to prevent further clinical manifestations of the disease continued unchanged until the end of the first World War. The introduction of experimental malaria therapy soon after its termination led to a clearer understanding of the natural history of malaria in man, while, as has been described, the synthesis of pamaquine in 1926 started a trickle, soon to become a stream, of new compounds lethal to the parasite. New methods

alike in its curative and preventive aspects, reflects the advances achieved by laboratory research. Twenty five years ago the prospects for radical prevention in falciparum infection were remote and prolonged courses of quinine were advocated for radical cure. Today, well timed therapy with minute doses of proguanil will eradicate *P. falciparum* at a pre-clinical stage in the human host, while a few days' therapy with one of the 4-aminoquinolines will usually cure the established infection. Falciparum malaria may now be suppressed with an ease and efficiency, with a safety and economy,

* See Selected bibliography No. 174-182 (page 114)

which must surely approach the ultimate limits of advance in this direction. But with vivax infection progress is less impressive. We lack a safe and sure preventive, though pyrimethamine may take us a step forward, and radical cure still depends on a prolonged treatment with drugs of moderate toxicity.

The Aims of Malaria Chemotherapy

1 *The life cycle of the parasite and the widening range of therapy*

From the account given in chapter 2 of the relation of its various phases to the mode of action of antimalarial drugs, it is clear that the malaria parasite lies open to attack by well directed therapy throughout most of its complex life-cycle. The sporozoite alone seems to be resistant. The schizogonic forms in the fixed tissues and circulating blood, the gametocytes and, through a carry-over effect, the sporogonic forms in the mosquito, are alike vulnerable to appropriate therapy, with differing effects on the course of infection (table IV).

TABLE IV CLINICAL RANGE OF MODERN THERAPY IN HUMAN MALARIA

Stage in life cycle of parasite	Clinical range of present day drugs
Schizogonic forms in fixed tissues	causal prophylaxis of falciparum infection before the parasites reach the blood radical cure of vivax infection
Schizogonic forms in the blood	termination of the acute attack radical cure of falciparum infection suppression of all forms of malarial infection suppressive cure of falciparum infection reduction in source of gametocytes with indirect effect on transmission
Gametocytes	direct effect on transmission

2 *Therapeutic resources*

The aims of malaria chemotherapy may now be more closely defined. Broadly, they remain what they have always been—to cure the patient sick with malaria and to prevent malaria or its clinical manifestations under all the varied circumstances in which they may appear. We think first of the individual. If he is exposed to infective mosquitos we aim to protect him by sterilizing infection while it is still symptomless, if he becomes

sick with malaria, to relieve his symptoms as speedily, as safely, and as comfortably as possible, with permanent cure of his infection. If he is a symptomless carrier, we aim to eradicate the infection, or, failing this, to suppress it at a continued subclinical level. For the community we aim to break the chain of transmission by directing treatment, curative and suppressive, toward the destruction of gametocytes or to the inhibition of their production or development.

The ideal drug would meet all these demands without harm to the patient. It would be quick in action and unvarying in its effects. It would be active in all forms of human malaria, at all stages, and it would not induce resistance in the parasites. Furthermore, it would be easy to administer by the oral or by the parenteral route, and it would be stable and cheap. No known drug satisfies all these exacting requirements, though most of them can be met by a judicious selection of the drugs now available.

The compounds which fill a useful role in malarial therapy are all members of four chemical groups—the 4-aminoquinolines and allied compounds, the 8-aminoquinolines, the biguanides, and the pyrimidines. Table V lists the compounds on which present-day therapy is mainly based.

TABLE V DRUGS ON WHICH PRESENT DAY MALARIA CHEMOTHERAPY IS BASED

Chemical group	Main members of the group	Activity
4-aminoquinolines and related compounds	chloroquine amodiaquine mepacrine quinine	Essentially schizontocides. Little action on exoerythrocytic parasites, or on the gametocytes of <i>P. falciparum</i> . The most useful drugs known for treating acute malaria; all except quinine are powerful suppressives. Low toxicity. Do not induce drug-resistance.
8-aminoquinolines	primaquine pamaquine	Poor schizontocides but active against gametocytes and against exoerythrocytic parasites. Main uses: gametocytocidal treatment and radical cure in vivax infection. Moderately toxic. Do not induce significant drug-resistance.
Biguanides	proguanil	Schizontocide and sporontocide. Active also against the exoerythrocytic forms of <i>P. falciparum</i> . Main uses: causal prophylaxis in falciparum infection; suppression and inhibition of sporogony. Non-toxic. Liable to induce drug-resistance.
Pyrimidines	pyrimethamine	Activity similar to that of proguanil but has some action also on the exoerythrocytic forms of <i>P. vivax</i> . Main uses: as for proguanil. Low toxicity. Liable to induce drug-resistance.

which must surely approach the ultimate limits of advance in this direction. But with vivax infection progress is less impressive. We lack a safe and sure preventive, though pyrimethamine may take us a step forward, and radical cure still depends on a prolonged treatment with drugs of moderate toxicity.

The Aims of Malaria Chemotherapy

1 *The life-cycle of the parasite and the widening range of therapy*

From the account given in chapter 2 of the relation of its various phases to the mode of action of antimalarial drugs, it is clear that the malaria parasite lies open to attack by well directed therapy throughout most of its complex life-cycle. The sporozoite alone seems to be resistant. The schizogonic forms in the fixed tissues and circulating blood, the gametocytes and, through a carry over effect, the sporogonic forms in the mosquito, are alike vulnerable to appropriate therapy, with differing effects on the course of infection (table IV).

TABLE IV CLINICAL RANGE OF MODERN THERAPY IN HUMAN MALARIA

Stage in life cycle of parasite	Clinical range of present-day drugs
Schizogonic forms in fixed tissues	causal prophylaxis of falciparum infection before the parasites reach the blood radical cure of vivax infection
Schizogonic forms in the blood	termination of the acute attack radical cure of falciparum infection suppression of all forms of malarial infection suppressive cure of falciparum infection
Gametocytes	reduction in source of gametocytes with indirect effect on transmission direct effect on transmission

2 *Therapeutic resources*

The aims of malaria chemotherapy may now be more closely defined. Broadly, they remain what they have always been—to cure the patient sick with malaria and to prevent malaria or its clinical manifestations under all the varied circumstances in which they may appear. We think first of the individual. If he is exposed to infective mosquitos we aim to protect him by sterilizing infection while it is still symptomless, if he becomes

sick with malaria, to relieve his symptoms as speedily, as safely, and as comfortably as possible, with permanent cure of his infection. If he is a symptomless carrier, we aim to eradicate the infection, or, failing this, to suppress it at a continued subclinical level. For the community we aim to break the chain of transmission by directing treatment, curative and suppressive, toward the destruction of gametocytes or to the inhibition of their production or development.

The ideal drug would meet all these demands without harm to the patient. It would be quick in action and unvarying in its effects. It would be active in all forms of human malaria, at all stages, and it would not induce resistance in the parasites. Furthermore, it would be easy to administer by the oral or by the parenteral route, and it would be stable and cheap. No known drug satisfies all these exacting requirements, though most of them can be met by a judicious selection of the drugs now available.

The compounds which fill a useful role in malarial therapy are all members of four chemical groups—the 4-aminoquinolines and allied compounds, the 8-aminoquinolines, the biguanides, and the pyrimidines. Table V lists the compounds on which present-day therapy is mainly based.

TABLE V DRUGS ON WHICH PRESENT DAY MALARIA CHEMOTHERAPY IS BASED

Chemical group	Main members of the group	Activity
4-aminoquinolines and related compounds	chloroquine amod aquine mefloquine quinine	Essentially schizontocides. Little action on asexual erythrocytic parasites, or on the gametocytes of <i>P. falciparum</i> . The most useful drugs known for treating acute malaria, except quinine, are powerful suppressives. Low toxicity. Do not induce drug-resistance.
8-aminoquinolines	primaquine pamaquine	Poor schizontocides, but active against gametocytes and against asexual erythrocytic parasites. Main uses: gametocytocidal treatment and radical cure in vivax infection. Moderately toxic. Do not induce significant drug-resistance.
Biguanides	proguanil	Schizontocide and sporontocide. Active also against the asexual erythrocytic forms of <i>P. falciparum</i> . Main uses: causal prophylaxis in falciparum infection, suppression and inhibition of sporogony. Non-toxic. Liable to induce drug-resistance.
Pyrimidines	pyrimethamine	Activity similar to that of proguanil, but has some action also on the asexual erythrocytic forms of <i>P. vivax</i> . Main uses: as for proguanil. Low toxicity. Liable to induce drug-resistance.

The Confusions of Dosage

A severe case of falciparum malaria may require 10,000 mg (150 grains) of quinine before the fever is controlled, an *evanescent febrile episode* in an old standing infection may be terminated by three or four tablets of aspirin. A proguanil sensitive falciparum infection may be clinically cured by a single proguanil tablet of 100 mg, a resistant infection may still persist when the patient has received 50 times this amount. These extreme examples illustrate the fallacies which may underlie attempts to fix arbitrary levels of dosage, suitable for all malaria infections, at all times, and in all places. Confusion arises mainly from the immunity factor in the therapeutic response, from differences in the geographical strains of the parasites, and from drug resistance.

1 *The immunity factor*

The response to treatment in malaria is usually, perhaps always, an expression of a dual effect. The plasmodicidal effect of the drug is reinforced by a contribution from the tissue defences. In the early stages of a primary infection in subjects with little immunity the contribution from the tissues may be small, in old standing infections the tissue defences may suffice of themselves to break the schizogonic cycle of the parasite. Logically, the dose of a drug should then be related to the immune status of the subject. Immunity, however, is not always easy to assess, and the dosage usually recommended is that appropriate for infection in the non immune subject. Medical officers, with their special knowledge of the malaria with which they have to deal, are best able to decide whether, and to what extent, they may safely reduce the dosage ordinarily recommended for treatment and suppression.

2 *Strain of parasite*

As noted elsewhere, geographical strains of malaria parasites sometimes differ in their sensitivity to a particular drug. Primaquine is more active against Korean vivax strains than against the New Guinea Chesson strain, the Costa strain of *P. falciparum* seems to be less sensitive to quinine and mepacrine than the McLendon strain of the same species, a Dutch strain of *P. vivax* has been shown to be less sensitive to Salvarsan than the Madagascar strain, which is probably of African or Asian origin and other examples have been recorded. The differences are seldom marked, and they do not appear to be common, but at least they show that a drug dosage may not necessarily have universal validity, and they may sometimes explain why a drug regimen which gives good results in one part of the world may be disappointing in another.

3 *Drug resistance*

Dosage is normally based on the response to treatment of fully sensitive parasites. Should the parasites become resistant, the recommended dosage might be seriously in fault. Fallacy from this source, however, is unlikely to arise with quinine, mepacrine, chloroquine, or amodiaquine, the drugs on which the treatment of acute infection is based. The only drugs giving rise to serious resistance are proguanil and pyrimethamine.

4 *Age and body-weight*

about 110 lb (50 kg) in weight, and individuals may weigh less than 100 lb (45 kg). The calculation of dosage on a body weight basis, taking 150 lb as the norm, is probably a sound rule. For children up to the age of 12 years, a modified Young's formula* gives a good approximation to the body weight dosage. Children tolerate antimalarial drugs quite well, and should there be uncertainty as to the dosage for serious infection, it is wiser to give too much rather than too little.

5 *Base or salt*

Another source of confusion is the practice of expressing dosage sometimes as the salt, sometimes in terms of the content of active base. A proprietary brand of chloroquine is marketed as tablets of 250 mg with no mention of the amount of active base; another brand, sold as tablets of 200 mg, has the base content printed in smaller type on the label, both contain 150 mg of chloroquine base. An amodiaquine tablet of 261 mg, on the other hand, contains 200 mg of active base, and no other figure appears on the label. The dosage of pamaquine is even more confused: an 18 mg tablet of the naphthoate and a 10-mg tablet of the dihydrochloride alike contain 8 mg of active base, but the figures which receive prominence are 18 mg and 10 mg. For the older drugs, like quinine, we shall continue to think of dosage in terms of the salt, but for the newer drugs there is no good reason for the persistence of this confusing anomaly. The logical course is to give all dosage in terms of the active base; no other figure should appear on manufacturers' labels. Where this is not possible, the dosage in terms of salt having been established by custom, the base content should at least be stated. The base content of the antimalarial salts in common use is given in Annex 2.

* Dosage for children = adult dosage $\times \frac{\text{age next birthday}}{\text{age} + 12}$

6 Comment

The drug dosage recommended throughout this account assumes that the patient is an adult weighing about 150 lb (70 kg), that he has no significant immunity to malaria, and that the parasites have no natural or acquired resistance. Under particular circumstances this dosage may be inappropriate. The physician alone, from his special knowledge of these circumstances, can evaluate the modification which may be necessary.

The Malaria Patient *

1. The simple acute infection

The primary clinical aim in acute malaria is to bring the attack to an end, quickly, safely, and with minimal discomfort to the patient. The symptoms are due to the rapid proliferation of asexual parasites in the blood, they must be destroyed. The most useful drugs for this purpose are the 4-aminoquinolines and related compounds (tables VI and VII). When these drugs are given at the recommended dosage, they may be

TABLE VI ADULT DOSAGE OF 4-AMINOQUINOLINES AND RELATED COMPOUNDS FOR THE SIMPLE ACUTE ATTACK

Drug	Dosage (mg) and days							Total
	1	2	3	4	5	6	7	
Chloroquine base or Amodiaquine base or	600 + 300 ^a	300	300	—	—	—	—	1 800 mg
Mepacrine or	600	400	400	—	—	—	—	1 400 mg
Quinine *	200 × 5 ^b	300	300	300	300	300	300	2 800 mg
	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	14 000 mg (210 grains)

^a Second dose 6 hours after first

^b Every 6 hours

* Quinine in divided doses. Some authorities reduce the daily dose to 20 grains after the first 2 days (total 160 grains).

Note. The dosages of antimalarial drugs recommended by workers in different countries shows considerable variation. For example in India it has been stated that a single dose of 600 mg of chloroquine or amodiaquine or a 3-day course of 20 to 30 grains of quinine daily will effect clinical cure in the majority of mild infections.

* In general this account is restricted to the specific treatment of malaria. Nursing management, relief of special symptoms and convalescence are in accord with general principles.

TABLE VII. PROPRIETARY PREPARATIONS AND SALTS OF DRUGS
RECOMMENDED FOR THE SIMPLE ACUTE ATTACK

Drug	Salt	Common proprietary names	Usual preparations
Chloroquine	diphosphate	Resochin Aralen Avictor	Tablets of 250 mg containing 150 mg of chloroquine base, dosage in terms of base
	monosulfate	Chloraquine	Tablets of 204 mg containing 150 mg of base or of 135 mg of salt containing 100 mg of base or of 408 mg of salt containing 300 mg of base, dosage in terms of base
Amodiaquine	dihydrochloride dihydrate	Camodia	Tablets containing 200 mg of base, dosage in terms of base
Mepacrine	dihydrochloride dihydrate	Atabrin Atabrine Quinacrine	Tablets of 100 mg containing 79% of base, dosage in terms of dihydrochloride dihydrate
Quinine	dihydrochloride or sulfate	—	Acid solution, dosage in terms of salt

expected to bring about a remission of symptoms within from one to three days and to eradicate most falciparum and ovale infections. Infections due to *P. vivax* or *P. malariae* are likely to recur. The treatment of relapsing infections is discussed in a later section (page 81).

The drugs are normally given by mouth but, should the patient be unable to retain the drugs because of nausea or vomiting, the whole or some part of the dose must be given by injection. In this event, oral treatment must be resumed as soon as possible. Parenteral treatment is discussed in the section on grave infection (page 77).

(a) The "loading dose"

has been the general synthetic compounds, Quinine attains a high serum concentration fairly quickly, moreover, heavy dosage would be unsound on clinical grounds, for these reasons quinine is given at a steady level throughout treatment. Mepacrine and the 4-aminoquinolines, on the other hand, reach their peak concentration in the serum more slowly, a delay which is effectively overcome by "loading" the dosage at the beginning of the course. There can be little doubt that therapy with the synthetic drugs is more rapidly effective today than it was with mepacrine before the second World War, and that the "loading dose" is largely responsible for the change.

(b) Chloroquine

This drug is probably unsurpassed by any known remedy for the treatment of the acute malaria attack. It has the same plasmodicidal range as mepacrine, but is more active and, unlike mepacrine, does not stain the skin. At normal dosage, its toxicity is very low. No contraindications to its use have been reported. The drug is issued under various proprietary names as tablets containing 100 mg, 150 mg, or 300 mg of chloroquine base.

(c) Amodiaquine

This drug closely resembles chloroquine in its antimalarial activity. The differences are probably too small to be clinically significant. The toxicity at therapeutic dosage is very low, no contraindications have been reported.

(d) Mepacrine

The value of mepacrine in the treatment of acute malaria was attested by extensive experience of the drug gained both before and during the second World War. It is reliable and rapidly effective, but not entirely free from disconcerting side effects. Temporary abdominal discomfort in the first few days of therapy, and a harmless yellow staining of the skin and eyes later on, are fairly common, rarely, the drug may induce mental symptoms varying from a mild depression or excitement to a wild mania, epileptiform convulsions have been reported with parenteral administration. The mental effects ("mepacrine psychoses") tend to clear up fairly

- - - - -
- - - - -
- - - - -

(e) Quinine

There is a prevailing tendency today to decry quinine. True, quinine has defects from which the newer synthetic remedies are free: it causes unpleasant cinchonism, it may occasionally precipitate blackwater fever, and it is less likely to eradicate infection. But, when all is said, for the immediate treatment of the acute infection, quinine remains a remarkably safe and effective drug.

For the treatment of the acute malaria attack, quinine is given in solution in capsules or as tablets of the dihydrochloride or sulfate in divided doses three or four times a day. Sugar-coated tablets are less unpleasant to the taste, they are usually efficient but they carry the off-chance of defective absorption. Children tolerate quinine very well and

seem to need relatively higher doses than adults. Serious toxic effects from therapeutic doses of quinine are extremely rare. Personal idiosyncrasy, and a history or threat of blackwater fever, are the main contraindications to its use. The termination of pregnancy during quinine treatment is far more likely to be due to the malaria than to quinine, but most doctors would probably wish to play for safety by using some other drug.

2. The grave infection

The clinically grave or parasitologically intense malaria infection is a medical emergency demanding immediate treatment and meticulous care until the danger is past. The cause is nearly always *P. falciparum*, rarely *P. vivax*. Warning symptoms may appear with alarming suddenness in the course of a simple falciparum attack and a few hours delay may mean the difference between life and death. The clinical and parasitological indications for regarding an infection as serious, or potentially serious, are coma or mental clouding, collapse, jaundice, severe vomiting or diarrhoea, high parasitaemia, and the presence of falciparum schizonts or very young gametocytes in blood films. *Every falciparum infection with more than 10% of the red cells infected is serious, however mild the symptoms. In these infections the microscope sometimes gives a more reliable indication of gravity than a clinical examination.*

When the patient with grave infection is conscious, co-operative, and able to swallow, he may be given oral treatment with the same drugs, and at the same dosage, as for the simple attack (page 74), but even in these cases many physicians prefer to give the first one or two doses by injection for greater assurance of prompt absorption. Coma, vomiting, and severe nausea are clear indications for administering by intramuscular or intravenous injection. Oral therapy should be substituted for parenteral therapy as soon as the danger is passed, and the patient is able to swallow the drugs and retain them.

The most effective drugs in these cases are quinine, chloroquine, amodiaquine, and mepacrine (table VIII). Conservative physicians of an older school would probably give this order of precedence, their younger colleagues would be more likely to give pride of place to chloroquine. There would probably be general agreement, however, that chloroquine is a better drug than quinine for intramuscular administration.

(a) Quinine

With the exception of mepacrine, all the drugs recommended for the treatment of grave falciparum infection may be given either by intramuscular or by intravenous injection. We must remember, however, that

(b) *Chloroquine*

This drug is probably unsurpassed by any known remedy for the treatment of the acute malaria attack. It has the same plasmodicidal range as mepacrine, but is more active and, unlike mepacrine, does not stain the skin. At normal dosage, its toxicity is very low. No contraindications to its use have been reported. The drug is issued under various proprietary names as tablets containing 100 mg, 150 mg, or 300 mg of chloroquine base.

(c) *Amodiaquine*

This drug closely resembles chloroquine in its antimalarial activity. The differences are probably too small to be clinically significant. The toxicity at therapeutic dosage is very low, no contraindications have been reported.

(d) *Mepacrine*

The value of mepacrine in the treatment of acute malaria was attested by extensive experience of the drug gained both before and during the second World War. It is reliable and rapidly effective, but not entirely free from disconcerting side effects. Temporary abdominal discomfort in the first few days of therapy, and a harmless yellow staining of the skin and eyes later on, are fairly common, rarely, the drug may induce mental symptoms varying from a mild depression or excitement to a wild mania, epileptiform convulsions have been reported with parenteral administration. The mental effects ('mepacrine psychoses') tend to clear up fairly quickly when the drug is withdrawn, and the convulsions, while alarming, disappear without harmful sequelae. Syphilis of the central nervous system⁶⁸ and a history of nervous system sequelae from previous mepacrine therapy, are contraindications to the use of the drug.

(e) *Quinine*

There is a prevailing tendency today to decry quinine. True, quinine has defects from which the newer synthetic remedies are free. It causes unpleasant cinchonism, it may occasionally precipitate blackwater fever, and it is less likely to eradicate infection. But, when all is said, for the immediate treatment of the acute infection, quinine remains a remarkably safe and effective drug.

For the treatment of the acute malaria attack, quinine is given in solution, in capsules or as tablets of the dihydrochloride or sulfate in divided doses three or four times a day. Sugar-coated tablets are less unpleasant to the taste, they are usually efficient but they carry the off-chance of defective absorption. Children tolerate quinine very well and

seem to need relatively higher doses than adults. Serious toxic effects from therapeutic doses of quinine are extremely rare. Personal idiosyncrasy, and a history or threat of blackwater fever, are the main contraindications to its use. The termination of pregnancy during quinine treatment is far more likely to be due to the malaria than to quinine, but most doctors would probably wish to play for safety by using some other drug.

2 The grave infection

The clinically grave or parasitologically intense malaria infection is a medical emergency demanding immediate treatment and meticulous care until the danger is past. The cause is nearly always *P. falciparum*, rarely *P. vivax*. Warning symptoms may appear with alarming suddenness in the course of a simple falciparum attack and a few hours delay may mean the difference between life and death. The clinical and parasitological indications for regarding an infection as serious, or potentially serious, are coma or mental clouding, collapse, jaundice, severe vomiting or diarrhoea, high parasitaemia, and the presence of falciparum schizonts or very young gametocytes in blood films. *Every falciparum infection with more than 10% of the red cells infected is serious, however mild the symptoms. In these infections the microscope sometimes gives a more reliable indication of gravity than a clinical examination.*

When the patient with grave infection is conscious, co-operative, and able to swallow, he may be given oral treatment with the same drugs, and at the same dosage, as for the simple attack (page 74), but even in these cases many physicians prefer to give the first one or two doses by injection for greater assurance of prompt absorption. Coma, vomiting, and severe nausea are clear indications for administering by intramuscular or intravenous injection. Oral therapy should be substituted for parenteral therapy as soon as the danger is passed, and the patient is able to swallow the drugs and retain them.

The most effective drugs in these cases are quinine, chloroquine, amodiaquine, and mepacrine (table VIII). Conservative physicians of an older school would probably give this order of precedence, their younger colleagues would be more likely to give pride of place to chloroquine. There would probably be general agreement, however, that chloroquine is a better drug than quinine for intramuscular administration.

(a) Quinine

With the exception of mepacrine, all the drugs recommended for the treatment of grave falciparum infection may be given either by intramuscular or by intravenous injection. We must remember, however, that

**TABLE VIII PROPRIETARY PREPARATIONS AND SALTS OF DRUGS
RECOMMENDED FOR PARENTERAL TREATMENT IN GRAVE INFECTION
(ADULT DOSAGE)**

Drug	Preparation and salts	Initial parenteral therapy	
		Intramuscular	Intravenous*
Quinine	Solutions of hydrochloride or dihydrochloride	—	—
Chloroquine	Resochin Aralen and Nivaquine are available in ampoules containing 5% of salt (approximately) 1 ml = 30-40 mg of base	Single dose not exceeding 10 ml of 5% solution of salt (300-400 mg of base). Total of 800 mg of base spaced over first 24 hours. Oral therapy as soon as possible	Recommended only when there are good clinical indications for intravenous infusion (see text). An effective blood level is rapidly attained by the safer and more convenient intramuscular route
Amodiaquine	Stable solutions not yet available	—	—
Mepacrine	Methanesulphonate	Single doses not exceeding 300 mg. Total in first 24 hours—600-800 mg. Oral therapy as soon as possible	Not recommended

* Intravenous infusions in saline, glucose, saline or plasma

** Winckel** recommends concentrated quinine-urethane or quinine antipyrin solutions for intramuscular injection. They are nearly neutral in reaction and cause less pain than acid solutions

whereas our knowledge of the use of quinine in these circumstances comes of a vast experience over many years, published information on the use of parenteral chloroquine, though very favourable, is still comparatively small. For this information we look to the physicians in tropical countries rather than to the experimental laboratories, and they have still to record a sufficient body of reliable evidence.

Intramuscular or intravenous quinine? There is no unanimity on the relative merits of intramuscular and intravenous quinine in malaria. Both methods have received authoritative support, though most experienced physicians today seem to favour the intravenous route. From the confused evidence the broad facts and opinions which emerge are

(1) that quinine injections should be given only when there are good reasons for them—grave infection, coma, digestive intolerance, defective absorption from the alimentary tract. Risks there are, and

though these risks cannot be justified for routine treatment, they must be taken when life is at stake,

(2) that intramuscular quinine always produces tissue necrosis and may leave fibrotic indurations which last for years, that faulty technique may lead to disastrous crippling, or even to death from tetanus, but that with sensible precautions as to the site of injection and the sterility of equipment and solutions these risks are very small,

(3) that intravenous injections of quinine cause a fall in blood-pressure, and carry a small risk of venous thrombosis at the site of injection and a remote risk of sudden death when the injection is given too quickly or when there is quinine hypersensitivity or threatening circulatory failure,

(4) that quinine acts rather more quickly when injected into the blood stream

Intramuscular quinine should be injected deep into the gluteal muscles An injection site about 3 inches (7.5 cm) below the centre of the iliac crest is anatomically safe. The skin should be thoroughly cleansed and scrupulous care taken to ensure the sterility of syringe, needle, and solution. The ampoules of quinine in concentrated solution prepared by manufacturers for injection are strongly recommended, their sterility is assured, and some of the best of them are especially compounded to give a solution nearly neutral in reaction. Single doses should not exceed 1,000 mg (15 grains), and they may with advantage be as small as 500 mg (7½ grains), the total dosage over 24 hours should not exceed 2,000 mg (30 grains). With these precautions, the danger of serious complications is exceedingly small.

The cardinal principles of intravenous quinine therapy are high dilution and slow administration. Fatalities have occurred from injections given at the rate often recommended—10 minutes for a 20-ml dose containing 650-1,000 mg (10-15 grains). The drug is far better given as a slow intravenous infusion in a litre of saline, glucose saline, or plasma. Strahan has drawn attention to the efficiency and safety of the continuous intravenous quinine "drip". His experience with grave falciparum infection among ill-nourished prisoners of war suggests that the hazards arising from intravenous quinine therapy are much reduced by this method of administration.*

* Non-specific therapy is far more important in these grave falciparum infections than in the simple attack. For intravenous transfusion the quinine may be given in normal saline, glucose saline or plasma. Some physicians recommend the addition of them or epinephrine or of Penicillin sodium for convulsions or coma. Transfusions of fresh blood may be necessary for severe anaemia from heavy destruction of red cells. Ransome's experience with a coma team in Burma during the second World War states that comatose cases do best when nursed in Fowler's position if the state of the circulation is satisfactory.

(b) *Chloroquine*

The clinical trials of intramuscular and intravenous chloroquine so far reported, though few in number, have been very favourable. The drug is said to be safe and effective when given by intravenous injection or infusion, and it has been suggested that intravenous administration might be the method of choice for the initial treatment of the patient who is seriously ill.¹⁸⁰ Rapid injection caused dizziness, nausea, disturbance of vision, and a transient fall in blood pressure, but these effects were almost eliminated when the drug was given by infusion in 500 ml of saline. The dose was 400 mg of chloroquine base.

Several reports have been published recording satisfactory results following intramuscular injections of chloroquine in single doses up to 300 mg of base. The injections were well tolerated, and speedy in their effects.^{175, 176, 181}

Intramuscular and intravenous injections of chloroquine are alike quickly effective, and in the present state of knowledge it seems that intramuscular administration, from its safety and convenience, will usually be the method of choice. The patient's state of fluid balance may well be a deciding factor. With obvious dehydration from vomiting, diarrhoea, or sweating, the clinical advantages of the intravenous infusion or continuous "drip" might outweigh other considerations.

(c) *Amodiaquine*

Since the two drugs resemble one another so closely as regards their antimalarial activity and toxicity, it seems probable that recommendations for the use of chloroquine in severe malaria will apply equally well to amodiaquine. It has been reported that amodiaquine is well tolerated when given intramuscularly and intravenously for simple attacks in doses up to 300 mg of base,^{177, 178} but there is little information on its merits for parenteral treatment in severe malaria. Until clinical experience has more fully confirmed the efficacy and safety of injections, the drug can be used with confidence for the patient who is seriously ill only when it is possible to give it by mouth.

(d) *Mepacrine*

Mepacrine is a well proved remedy in severe malaria. Like all antimalarial drugs, it is best given by mouth. Intramuscular injections of the soluble methanesulfonate are very effective and reasonably safe, intravenous administration is inadvisable as the safety margin is small. The dose for a single intramuscular injection should not exceed 300 mg nor the total dose exceed 900 mg for the first 24 hours. The drawbacks are those

associated with simple oral therapy, with the added small risk of epileptiform convulsions occurring soon after the injections. The convulsions are alarming but they soon pass and seem to have no serious sequelae.

3. The relapsing or recrudescent infection

When a malaria infection has been treated and apparently cured, a recurrence of symptoms means that the treatment has either failed to eliminate all the asexual parasites in the blood, or, having cleared the blood completely, has failed to destroy the persisting forms in the fixed tissues. Relapses in falciparum infections are attributed to the persistence of a few asexual parasites in the blood despite treatment, they may occur, though not very often, after treatment with any of the 4-aminoquinolines and allied drugs, particularly quinine. Relapses in vivax infections, on the other hand, are thought to be due to secondary exoerythrocytic forms which resist the ordinary schizontocidal drugs and survive treatment; they are very common after treatment based solely on the 4-aminoquinolines or allied compounds. The presumed origin of relapses in malaria may be represented as follows:

P. falciparum

Primary e-e forms → Asexual blood forms causing primary attack and recrudescences

P. vivax

Primary e-e forms → { Asexual blood forms causing primary attack
Secondary e-e forms → Asexual blood forms causing relapses

The treatment of relapses in malaria recognizes these differences of origin. Infection due to *P. falciparum* is finally cured by eradication of the asexual blood forms, vivax infections by eradication of both the asexual blood forms and of the secondary exoerythrocytic parasites in the fixed tissues.

(a) Recrudescent falciparum infection

The asexual blood cycle of *P. falciparum* is usually eliminated by the 4-aminoquinolines and similar drugs given at doses appropriate for the acute attack, but falciparum infections do sometimes recrudesce, particularly after quinine treatment. They should be treated like any other acute attack, and they may be prevented by a follow up treatment at suppressive dosage with any good schizontocidal drug (See section on after treatment, page 84.)

this procedure was first suggested by Sinton & Bird²¹ in India, who used a combination of pamaquine with quinine. This was the standard treatment for the radical cure of vivax malaria until 1945, when primaquine was synthesized by American investigators in the course of their search for a less toxic drug. Primaquine appears to be not only less toxic, but also more active than any of the 8 aminoquinolines yet tested. The usual course of treatment lasts 14 days, against refractory infections treated at

TABLE IX ADULT DOSAGE OF 8-AMINOQUINOLINES FOR RADICAL CURE IN VIVAX INFECTION

Drug	Dosage	
Primaquine base or Pamaquine base	15 mg daily for 10-14 days 8-10 mg thrice daily for 10-14 days	combined with standard treatment with chloroquine, amodiaquine or quinine if an overt attack is in progress

Radical cure of vivax infections with primaquine may also be attempted during latency with primaquine alone—15 mg daily for 14 days⁴³

Patients taking any of the 8 aminoquinolines should be under daily supervision because of the occasional unpredictable occurrence of acute intravascular haemolysis. Cyanosis, abdominal pain, the passage of dark urine, and maybe fever, are the warning signs.

4 The dispensary patient

The drug or the treatment best adapted to the needs of the malaria patient in hospital is not necessarily suitable for the dispensary outpatient. Dispensary patients report for fever, they will probably wish to return home, and they may not be seen again. Treatment must therefore be simple and safe, it must be effective in doses which can be taken at the time of the visit, and it must be cheap. The single dose therapy possible with some of the newer drugs meets most of these demands. The partial immunity which many of these patients have, particularly in tropical countries, helps the clinical response, and a clinical cure, sometimes a radical cure, may be expected. The most useful drugs are chloroquine (Resochin, Nivaquine, Aralen, or Avloclor), and amodiaquine. Recommended doses are shown in table X.

TABLE X SINGLE DOSE THERAPY FOR DISPENSARY PATIENTS

Drug	Dosage (mg) and age (years)					
	adult	over 12	6-12	3-6	1-3	under 1
Chloroquine or Amodiaquine	600 base 600 base	450-600 400-600	450 400	300 300	225 200	37.75 100-150

Single dose treatment with proguanil has proved effective in certain countries and good results have also been reported with pyrimethamine given in the same manner. In view of the possibility of drug resistance arising with both proguanil and pyrimethamine, it seems wiser to reserve these drugs exclusively for prophylaxis and suppression.

Single doses of mepacrine sometimes fail, and single doses of quinine usually fail. These drugs are hence unsuitable for single dose therapy. They should be used only when no other drugs are available and then be given over several days. The doses recommended for adults are shown in table XI.

TABLE XI ADULT DOSAGE OF MEPACRINE AND QUININE FOR DISPENSARY PATIENTS

First dose at dispensary	8 hours later	Daily for the next 3 days
Mepacrine—400 mg Quinine salt—1 000 mg (15 grains)	200 mg 1 000 mg (15 grains)	300 mg (in one dose) 1 500 mg (23 grains) (in divided doses)

5 After treatment

The primary aim of the treatment recommended for the simple, the grave, and the relapsing infection, is the speedy and safe cure of the attack, with such permanence as is possible with modern drugs given at practical dosage. Specific after treatment ensures that the patient is not infective to mosquitos when he leaves hospital, and raises the odds of permanent cure.

(a) *Falciparum* infection

Radical cure is probable with any of the schizontocidal treatments recommended for the acute attack, but freedom from early relapses may be further assured by a "follow up" regimen continuing for one month at suppressive dosage: chloroquine base—300 mg weekly, amodiaquine

base—400 mg weekly, proguanil salt—100 mg daily, or pyrimethamine—25 mg weekly (See also section 3, (a))

In cases where it is considered desirable to sterilize the gametocytes, specific after treatment is necessary, for the 4-aminoquinolines and similar drug

pam
for

treatment may begin when the temperature has fallen to normal or at the end of schizontocidal treatment, depending on the clinical condition of the patient. Delay is perhaps wise if the patient has been seriously ill, for primaquine and pamaquine contribute nothing to recovery and the slight hazard of early combined therapy serves no useful purpose.

(b) *Vivax* infection

Suppressive after treatment which will give the patient an assured freedom from a recurrence of fever, at least for a time, is recommended when the attack has been treated with schizontocidal drugs alone. Suitable drugs and doses are: pyrimethamine—25 mg weekly, proguanil salt—100 mg daily, chloroquine base—300 mg weekly, amodiaquine base—400 mg weekly, or mepacrine—100 mg daily. Suppressive therapy may conveniently begin ten days after the completion of treatment for the attack, and continue for two months. Whether suppression for a longer period is justified must depend on the circumstances of the patient. (See also section 3, (b) and (c))

6 Blackwater fever

In the early stages of blackwater fever, malaria parasites may be found in about half the cases, but as haemolysis proceeds they often disappear. When parasites are demonstrable in the blood, chloroquine, proguanil, or mepacrine should be given at normal dosage; if parasites are not found, suppressive therapy should be maintained into convalescence and a full course given when the clinical condition of the patient justifies it. Quinine, pamaquine, and primaquine are contraindicated.

The Symptomless Carrier

The malaria carrier who has no symptoms poses a variety of problems for which chemotherapy today often has an appropriate answer, but the answer may be determined more by circumstances than by the status of the individual infection. Broadly, three courses are open: to cure the infection, to suppress it, or to let it 'burn out'.

1 *The latent vivax infection*

Curative therapy is desirable if the patient is not exposed to re infection, and if it is practical under the patient's particular conditions of life. Primaquine—or, if this is unobtainable, pamaquine—should be given at full dosage without a schizontocide. The marginal toxicity of these drugs and the need for supervision are limiting factors. If curative treatment is inexpedient, suppression is the best alternative. Pyrimethamine, at a dosage of 25 mg once a week, is probably the best suppressive drug, continued for at least eight weeks it may sometimes result in suppressive cure. Sometimes these infections may be left to burn themselves out. Most physicians in the tropics have seen highly refractory vivax infections which resist all curative treatment. They have then to decide whether to suppress the infections indefinitely, or to leave the patient to work out his own salvation, protected only by schizontocidal treatment for late attacks.

2 *The "blood positive" carrier*

Curative therapy or suppression are the alternatives, with gametocyte therapy in addition for "crescent" carriers. Circumstances will decide the appropriate course. Curative therapy is indicated when re-infection is unlikely.

3 *The patient with splenic enlargement*

Parasites may or may not be demonstrable in the blood of the symptomless patient with an enlarged malarial spleen. These patients are usually semi-immunes in endemic areas. Suppressive therapy, efficiently applied over a few months, will markedly reduce the size of most malarial spleens.

Individual Drug Prophylaxis

Simple though the concept of malaria prevention by drugs may be, the application of preventive therapy to the varied needs of the person exposed to, or infected with, the malaria parasite is far from simple. If an individual wishes to live in a malarious country and remain healthy, he will ask to be protected against all forms of malaria. He may wish for protection to cover a short exposure, with protective therapy nicely timed to the period of risk, or for continuous protection during prolonged exposure, if infected, he will ask to be cured, or at least protected from the clinical manifestations of infection. Most of these demands can be met by use of the drugs now available.

1 General protection

The suppression of symptoms is perhaps the most useful clinical benefit conferred by regular and prolonged administration of small doses of anti-malarial drugs, but it is not the only benefit. Some infections are cured, and with particular drugs some are eradicated before they reach the blood stream. The term *general protection* is used here to include suppression, suppressive cure, and causal prophylaxis. The drugs commonly used are listed in table XII. Given at the dosage recommended these drugs are efficient suppressives in all forms of malaria, and, with the possible exception of quinine, they are all likely to cure falciparum infection within about a month. Proguanil and pyrimethamine in addition will usually eradicate falciparum infection at its source in the fixed tissues. None of these drugs is likely to eradicate vivax infection with the possible exception of pyrimethamine, which appears to have achieved suppressive cure in some cases against a particular strain of parasite.

TABLE XII DOSAGE OF VARIOUS DRUGS FOR GENERAL PROTECTION

Drug	Interval	Dosage (mg) and age (years)					
		over 16	11-16	7-10	4-6	1-3	under 1
Proguanil salt* or	daily	100	100	75	50	50	25
Chloroquine base	weekly	300	225	150	100	75	37
Amodiaquine base or	weekly	400	300	200	133	100	—
Mepacrine** or	daily	100	75	50	25	—	—
Pyrimethamine* or	weekly	25	25	16	12	8	—
Quinine salt†	daily	500-650 (8-10 grains)	300-500 (5-8 grains)	200-250 (3-4 grains)	130-200 (2-3 grains)	130 (2 grains)	65 (1 grain)

When protection is required for a limited period only drug administration should be continued for one week after the last day of exposure in the case of proguanil and pyrimethamine and for one month in the case of all other drugs.

* Contraindicated in areas where the prevailing malaria is known to be resistant to either of these drugs.

** Beginning 10 days before exposure to infection. With the other drugs listed it is unnecessary to begin the course earlier than the first day of exposure.

† Recommended only when other drugs are not available.

Of the drugs listed, proguanil is a causal prophylactic against falciparum infection, and is a good suppressive and an active sporontocide in all forms of malaria, its toxicity is very low. Its tendency to provoke resistance has been discussed in chapter 4 (page 59). In parts of Africa

the doses recommended in table XII have proved insufficient for clinical protection, and double this dosage may be necessary in such areas

Chloroquine and amodiaquine are powerful suppressants and will achieve suppressive cure in falciparum infection, their toxicity is low, and they do not provoke drug resistance. They are inactive against the pre erythrocytic forms of *P. falciparum* and have no inhibitory effect on sporogony

Mepacrine resembles chloroquine and amodiaquine in its clinical range but is somewhat less active and not entirely free from toxic side effects. Though a thoroughly reliable drug for clinical protection, it can no longer be recommended when the more effective 4-aminoquinolines are available

Pyrimethamine has very much the same activity as proguanil, but in addition will sometimes achieve suppressive cure with certain strains of *P. vivax*, its toxicity is low. Its tendency to provoke resistance has been discussed in chapter 4 (page 58)

Quinine, though a useful drug for clinical protection and still highly regarded in some countries by persons of conservative habit, is less efficient than the synthetic compounds mentioned above and can be recommended only when these are not available. Its mode of action resembles that of the 4-aminoquinolines and of mepacrine

2 Causal prophylaxis

With some of the modern drugs it is possible to eradicate malaria infections at their source in the fixed tissues, but the application, in the field and in hospital practice, of this radical form of prevention (the *causal prophylaxis* of James) is restricted by specific differences in the parasites and by the toxicity of some of the drugs. The prospects in falciparum malaria are very good, in vivax malaria they are poor, while in malariae and ovale malaria they are not fully known. Proguanil and pyrimethamine given at the doses listed in table XII are safe and highly efficient causal prophylactics in falciparum infection, failing only with strains which are resistant to these drugs. But all the drugs listed are comparatively inert against the pre erythrocytic forms of *P. vivax*, and causal prophylaxis in vivax infections has been attained only with the 8 aminoquinolines, particularly pamaquine and primaquine. Given at about the time of the infecting bite, pamaquine and primaquine will eradicate infection at the source, but the time of the infecting bite is seldom known and both drugs are too toxic for prolonged administration

3 Toxicity of antimalarial drugs

Any drug which has to be taken over a long period must be free from serious side-effects. At the dosage appropriate for prophylaxis, proguanil

is non toxic, pyrimethamine, given continuously in doses of the order of 25 mg daily, has a reversible depressive effect on the bone marrow, but the dose recommended for prophylaxis is so extremely small that the risk of toxic effects is remote, chloroquine and amodiaquine carry no known risk of any consequence. Mepacrine stains the skin and conjunctivae, and sometimes causes a lichenoid dermatitis, while psychoses occurring during suppressive administration have been reported. Quinine has a wide margin of safety, but sometimes causes unpleasant cinchonism. More detailed information regarding the toxicity of individual compounds is given in chapter 3. All in all, the risks of harmful side-effects from prophylaxis based on these drugs are small, particularly when they are assessed in the light of the benefits the drugs confer. Only with mepacrine and quinine are these effects ever likely to discourage wide scale use.

Collective Drug Prophylaxis

Malaria in a community reflects a biological relationship between malaria parasites, their human hosts, and the mosquitos which bring them together. Eliminate the mosquitos, or break their contact with man, and malaria disappears. Most large-scale malaria-control projects take advantage of these facts. Eliminate the parasites, or interrupt their life-cycle at

stances it may be almost complete

1 Principles

So long as personal drug prophylaxis is restricted to a few individuals, its effect on the malaria of the community to which they belong will be incidental and probably small. But when personal prophylaxis is spread so widely as to become collective prophylaxis a new series of effects, cumulative and highly significant for the community, contribute to the reduction or elimination of the seed bed from which the mosquitos derive their infection. Personal drug prophylaxis depends essentially on the interruption of the asexual cycles of the parasite, collective drug prophylaxis brings into play an additional action on gametogony and sporogony, with an interruption in the transmission of infection to mosquitos. The factors

Suppression by chloroquine

<i>Effect on asexual blood cycle</i>	<i>Collateral effect on gametocyte reservoir</i>
(a) Suppressive cure of falciparum infection	None at first, later, with cessation of attacks, no further production
(b) Suppression of vivax and malariae infection	Existing gametocytes destroyed, with cessation of attacks no further production

Causal prophylaxis and suppression by proguanil

<i>Effect on asexual cycles in blood and tissues</i>	<i>Collateral effect on gametocyte reservoir</i>
(a) Prevention of falciparum infection	No production
(b) Suppressive cure of existing falciparum infection	Sporogony inhibited, with cessation of attacks, no further production of gametocytes
(c) Suppression of vivax and malariae infection	

Since amodiaquine and mepacrine resemble chloroquine in their effects, whilst pyrimethamine in most respects resembles proguanil, these drugs given efficiently to every member of a closed community might be expected on theoretical grounds to arrest transmission completely, but practical difficulties limit their effect. Communities are seldom isolated from outside sources of infection, and the administration of any drug with unfailing regularity to every member of a community is an exacting task. The collateral effects of collective drug prophylaxis on the transmission of infection will hence be related to the epidemiological situation, and to the proportion of the community under regular drug protection.

2 Drugs and dosage

The continuous administration of a good schizontocide to a whole population, with dosage intervals related to the potency and persistence of the drug in the body, is theoretically the most effective method of collective drug prophylaxis. Initial "mass" or "blanket" therapy at a dosage appropriate for acute attacks is sometimes recommended but is seldom necessary. Other methods of administration—intermittent "mass" or "blanket" treatments at intervals of weeks or months, and selective treatments for parasite carriers—have usually been less successful. Collective drug prophylaxis based on pamaquine has been generally abandoned, but the possibilities in this field of the more active and less toxic 8-aminoquinoline, primaquine, have yet to be defined.

For the community, as for the individual, the most suitable drugs are proguanil, chloroquine, amodiaquine, mepacrine, and pyrimethamine. Table XIII summarizes the dosage recommended.

TABLE XIII. ADULT DOSAGE OF VARIOUS DRUGS
USED FOR COLLECTIVE PROPHYLAXIS*

Drug	Communities with little immunity, armies in the field, etc	Communities in endemic areas
Proguanil †, or	100 mg salt daily	200 mg salt twice a week or 300 mg salt once a week
Chloroquine, or	300 mg base once a week	300 mg base once in 1-2 weeks
Amodiaquine or	400 mg base once a week	400 mg base once in 1-2 weeks
Mepacrine or	100 mg daily	200 mg twice a week or 300 mg once a week
Pyrimethamine, ‡ or	■ mg once a week	25 mg once a week
Quinine §	650 mg (10 grains) daily	300 mg (■ grains) daily

* The doses for children are summarized in table XII

† Contraindicated in areas where the prevailing malaria is known to be resistant to either of these drugs

‡ A daily dose of 200 mg has been found necessary in parts of Africa

§ Recommended only when other drugs are not available

3 Indications for collective drug prophylaxis

The most successful and indeed the only lasting methods of malaria control in stable communities are those which depend on action against the insect vectors. There is little or no evidence that malaria can be completely and permanently controlled by drugs. But mosquito control is

UNUS*

(a) that mosquito control is the most successful form of permanent malaria control,

(b) that collective drug prophylaxis is always the method of choice for mobile groups operating in malarious country;

(d) that the application of collective drug prophylaxis in stable populations is justified only when more permanent methods are impracticable or disappointing

Collective drug prophylaxis has important limitations. It is likely to be successful only when the regularity of administration can be assured, and it is justified only when the malaria cannot be controlled at comparable trouble and expense by measures directed against the mosquito. Adequate supervision for the administration of drugs is possible only in populations which are fairly concentrated and under some form of discipline, such as armies in the field, labour gangs operating in malarious country, or plantation populations, and it is in these groups that collective drug prophylaxis achieves its most satisfying results.

The possibilities of collective drug prophylaxis in rural communities are less impressive. It can seldom be efficiently applied and is beset with administrative and other difficulties, it remains, however, the quickest method of bringing an epidemic under temporary control.

4 Control of epidemics

Severe epidemic malaria demands quick action: many people are sick, a few maybe are dying, and the immediate situation can be met by drugs alone. Collective drug prophylaxis, starting with a loading dose, has here one of its clearest indications. The drugs and doses recommended are summarized in table XIV.

TABLE XIV ADULT DOSAGE OF VARIOUS DRUGS
FOR THE EMERGENCY CONTROL OF EPIDEMIC MALARIA

Immediate single dose	Follow up continuous dosage
Chloroquine—600 mg base or Amodiaquine—600 mg base	Chloroquine—300 mg base weekly or Amodiaquine—400 mg base weekly or
If these drugs are not available use	Proguanil ^a —100 mg salt daily or
Mepacrine—400 mg	Mepacrine—100 mg daily or Pyrimethamine ^a —25 mg weekly

^a Contraindicated in areas where the prevailing malaria is known to be resistant to either of these drugs.

For individuals with fever at the time of examination, a single dose of chloroquine, amodiaquine or mepacrine is sometimes inadequate, further treatment with 300 mg daily for two days is desirable. The persons distributing the drugs should ensure that the full dose is swallowed and washed down with a drink of water. This precaution, a wise one at all times in collective drug prophylaxis, has a special importance during epidemics.

When the malaria is under control, a reduction of the follow up dosage of proguanil or mepacrine to 200 mg twice a week, or 300 mg once a week, may be considered. Drug administration should continue for at least one month—long enough for a suppressive cure of most falciparum infections. The likelihood of recrudescence vivax and malariae infections occurring some weeks after discontinuing the drugs should not be forgotten.

The emergency distribution of drugs should not replace or delay other and more lasting forms of control. House-spraying with residual insecticides should begin at once, and steps be taken to ascertain the cause of the epidemic. Whether drugs should or should not play any part in future control policy must depend on the prevailing conditions and available resources.

ANNEXES

ANNEX 1

SUMMARY OF SUGGESTED DOSAGE

Note The doses suggested in this summary are for adults of approximately 150 lb (70 kg) body-weight. In general they should be adjusted according to the usual rules for weight and age. The doses recommended for prophylaxis and suppression in children are given in table XII.

Treatment of clinical attack in non immune subjects

- (1) Chloroquine diphosphate or sulfate: 600 mg of base, 300 mg 6 hours later; 300 mg daily for next 2 days, or
- (2) Amodiaquine dihydrochloride dihydrate 600 mg of base first day, 400 mg daily for next 2 days, or
- (3) Mepacrine dihydrochloride dihydrate 1,000 mg (3 doses of 200 mg) first day, 100 mg thrice daily for next 6 days, or
- (4) Quinine sulfate or dihydrochloride 1,300-2,000 mg (20-30 grains) daily for 5-7 days

Emergency treatment

(1) Quinine dihydrochloride 650 mg (10 grains) in normal saline, glucose saline, or plasma, injected intravenously *very slowly* (not more than 50 mg of salt per minute), repeated in 6 hours if necessary, not more than 3 injections in 24 hours. Or administered by intravenous drip, at the rate of 2,000 mg (30 grains) in 24 hours. Oral therapy as soon as possible, or

(2) Mepacrine methane sulfonate given intramuscularly in single doses not exceeding 300 mg, total in first 24 hours, 600-900 mg. Oral therapy as soon as possible, or

the intramuscular route, which is generally to be preferred. Oral therapy as soon as possible

the intramuscular route, which is generally to be preferred. Oral therapy as soon as possible

Radical cure of vivax and malariae infection

(1) Primaquine diphosphate 15 mg of base daily in single or divided doses, for 14 days, reinforced by standard treatment with a schizontocidal drug* if given during an acute attack, or

(2) Pamaquine naphthoate or monohydrochloride 210 mg of base thrice daily for 10-14 days, reinforced by standard treatment with a schizontocidal drug* if given during an acute attack.

* Mepacrine should not be given concurrently with any of the 8-aminoquinoline drugs

Treatment of clinical attack in semi immune subjects

- (1) Chloroquine diphosphate or sulfate 600 mg of base, single dose; or
- (2) Amodiaquine dihydrochloride dihydrate 600 mg of base, single dose, or
- (3) Mepacrine dihydrochloride dihydrate 400 mg, 200 mg 4 hours later, 300 mg daily for next 3 days, or
- (4) Quinine sulfate or dihydrochloride 1,000-1,500 mg (15 ■ grains) daily for 2-5 days

*Prophylaxis and suppression **

- (1) Chloroquine diphosphate or sulfate 300 mg of base once weekly, or
- (2) Proguanil monohydrochloride ** 100 mg daily,† or, for partially immune subjects, 300 mg once weekly, or
- (3) Amodiaquine dihydrochloride dihydrate 400 mg of base once weekly, or
- (4) Pyrimethamine ** 25 mg once weekly, or
- (5) Mepacrine dihydrochloride dihydrate 100 mg daily, or, for partially immune subjects, 300 mg once weekly *Administration beginning 10 days before exposure to infection, or*
- (6) Quinine sulfate or dihydrochloride 650 mg (10 grains) daily *Recommended only when none of the above listed drugs ■ available*

* The prophylactic regimen should be continued for one week after leaving an endemic area where proguanil or pyrimethamine has been used and for one month in the case of other drugs

** The use of proguanil or pyrimethamine is contraindicated in areas where resistance to either of these drugs is known to exist

† In parts of Africa this dosage has been found insufficient in Nigeria, for instance the following scale has been recommended: adults, 100-200 mg daily, children 0-1 year 50 mg three to six times weekly 1-3 years 50 mg daily, over 3 years 100 mg daily

ANNEX 2

BASE-CONTENT OF TABLETS

Each 261 mg tablet of amodiaquine dihydrochloride dihydrate salt contains 200 mg of base

Each 250-mg tablet of chloroquine diphosphate salt contains 150 mg of base

Each 500-mg tablet of chloroquine diphosphate salt contains 300 mg of base

Each 204-mg tablet of chloroquine sulfate salt contains 150 mg of base

Each 136 mg tablet of chloroquine sulfate contains 100 mg of base

Each 408 mg tablet of chloroquine sulfate contains 300 mg of base

Each 100-mg tablet of mepacrine dihydrochloride dihydrate contains 78.5 mg of base

Each 360-mg ampoule of mepacrine methanesulfonate contains the equivalent of 300 mg of mepacrine dihydrochloride dihydrate

Each 120-mg ampoule of mepacrine methanesulfonate contains the equivalent of 100 mg of mepacrine dihydrochloride dihydrate

Each 18 mg tablet of pamaquine naphthoate 10-mg tablet of pamaquine dihydrochloride or 9 mg tablet of pamaquine monohydrochloride contains 8-mg of base. For practical purposes 2 naphthoate = 1 base = 1 mono- or dihydrochloride

Each 13.2 mg tablet of primaquine diphosphate contains 7.5 mg of base

Each 100-mg tablet of proguanil monohydrochloride contains 87 mg of base

Pyrimethamine is prescribed in the form of base, *not* as a salt

ANNEX 3

PHYSICAL DATA REGARDING SALTS

<i>Drug</i>	<i>Salt</i>	<i>Base-content (%)</i>	<i>Solubility in cold water* (g per 100 ml)</i>	<i>Stable or unstable in aqueous solution</i>
Quinine	sulfate	82.84	0.125	stable
	bisulfate	58-62	10	stable
	dihydrochloride	79-82	167	stable
	hydrochloride	81-83	3.1	stable
Chloroquine	diphosphate	62	at least 100	stable
	sulfate	76.5	33.3	stable
	hydrochloride	90	33.3	stable
Amodiaquine	dihydrochloride dihydrate	75.8	at least 20	unstable
Mepacrine	dihydrochloride	78.5	2.5	unstable
	dihydrate			
	dimethanesulfonate	65.5	33.3	stable but should not be stored for any length of time
Proguanil	monohydrochloride	WE	1	stable
Pyrimethamine	base	100	insoluble	—
Pamaquine	naphthoate	45	insoluble	—
	monohydrochloride	89.5	at least 20	stable but should be stored under inert gas and in the dark
Primaquine	diphosphate	57	at least 100	stable but some decomposition may take place on exposure to air and light

* i.e., 20° C

ANNEX 4

SYNONYMS OF ANTIMALARIAL DRUGS

Amodiaquine

CAM-AQ1
Cam-aqi
Camoquin
Flavoquine
Miaquin
SN 10751

Chloroquine

- Aralen
- Avloclor
- Nivaquine B
- Resochin
- Tanakan
- SN 7618
- 3377 RP

Mepacrine

Acniquine
Anchin
Atabrine
Atatrin
Atebrin
Atebrino
Chemiochin
Chinacrin
Chinacrine
Crinodora
Eriou
Haffkinone
Italchina
Malsaricida
Methoquine
Metoquina
Metoquine
Palacrin
Palusan
Quinsacrine
SN 390

Pamaquine

Aminoquin
Beprochin
Gamafar
Pamaquin
Plasmochin
Plasmoquine
Praequios
SN 971

Primaquine

SN 13172

Proguanil

Bigumal
Chloroguanide
Chloroguanone
Digmanyl
Drinupal
Guanatol
Paludrine
Palusi
Tirisan
M 4338
SN 12837

Pyrimethamine

Daraprim
Malocide
B-W 50-63

Santoquine

Nivaquine A
Nivaquine □
Santochin
Santoquine
Soutochin
SN 6911
3038 RP

* Aralen and Avloclor are chloroquine diphosphate

•• Nivaquine B, or Nivaquine, is chloroquine sulfate

SELECTED BIBLIOGRAPHY

SELECTED BIBLIOGRAPHY

Definition of Terms

- 1 COVELL, G., RUSSELL, P. F. & SWELLENHUBEL, N. H.
Malaria terminology, Geneva, 1953 (*World*

Health Organization Monograph Series, No 13)

Rationale of Malaria Chemotherapy

2. CHRISTOPHERS, S. R. & FULTON, J. D.
Observations on the respiratory metabolism of malarial parasites and trypanosomes
Ann trop Med Parasit 1938, 32, 43-75

- 3 COATNEY, R. & COOPER, W. C.
Recrudescence and relapse in vivax malaria
In *Proceedings of the Fourth International Congress on Tropical Medicine and Malaria*, Washington, D. C., United States Government Printing Office, 1948, vol. 1, pp. 629-639

- 4 COVELL, G. et al.
Studies on a West African strain of *Plasmodium falciparum* II The efficacy of Paludrine (proguanil) as a therapeutic agent
Trans roy Soc trop Med Hyg 1949, 42, 465-476

- 5 DAVEY, D. G.
Chemotherapy of malaria
Brit med Bull 1951, 8, 37-46

- 6 DÍAZ DE LEÓN, A.
Primeros casos de paludismo tratados por un derivado de la sulfanilamida
Boletín sanit panamer 1937, 16, 1039-1040
Treatment of malaria with sulfonamide compounds
Publ Hlth Rep (Wash.), 1937, 52, 1460-1462

- 7 FAIRLEY, N. H. et al.
Chemotherapeutic suppression and prophylaxis in malaria: an experimental investigation undertaken by medical research teams in Australia
Trans roy Soc trop Med Hyg 1945, 38, 311-363

- 8 FAIRLEY, N. H. et al.
Researches on Paludrine (M 4888) in malaria: an experimental investigation undertaken by the L H Q Medical Research Unit (A I F), Cairns, Australia
Trans roy Soc trop Med Hyg 1946, 40, 105-162

- 9 FIELD, J. W.
Notes on the chemotherapy of malaria, Kuala Lumpur, Federated Malay States Government Press 1939 (Bulletins from the Institute for Medical Research, Federated Malay States, No. 2 of 1938)

- 10 GARNHAM, P. C. C.
The mosquito transmission of *Plasmodium* and *Halbertsdier* & Prowazek, and its pre-erythrocytic development in the liver of the rhesus monkey
Trans roy Soc trop Med Hyg 1931, 45, 45-52

- 11 GARNHAM, P. C. C. et al.
Pre-erythrocytic stages of human malaria
Plasmodium ovale: A preliminary note
Brit med J 1934, 2, 257

- 12 GREENBERG, J.
The potentiation of the antimalarial activity of chloroquine by *p*-aminobenzoic acid competitors
J Pharmacol 1949, 97, 238-242

13. GREENBERG, J., BOYD, B. L. & JOSEPHSON, E. S.
Synergistic effect of chloroquine and sulfinadiazine against *Plasmodium gallinaceum* in the chick
J Pharmacol 1945, 94, 60-64

CHEMOTHERAPY OF MALARIA

- 14 GUTTMANN, P & ENRICH, P
Ueber die Wirkung des Methylenblau bei
Malaria *Berl Klin Wschr* 1891, 28,
953 956
- 15 HUTT, C G & COULSTON, F
The development of *Plasmodium gallinae*
from sporozoite to erythrocytic
trophozoite *J Infect Dis* 1944, 75,
231 249
- 16 JAMES S P et al
Discussion Synthetic antimalarial remo-
dies and quinine *Trans roy Soc trop
Med Hyg* 1932, 26, 105 138
- 17 JAMES S P & TATE, P
New knowledge of the life-cycle of malaria
parasites *Nature (Lond)* 1937, 139, 545
- 18 JAMES, S P & TATE, P
Exo-erythrocytic schizogony in *Plasmodium
gallinaceum* Brumpt, 1935 *Parasitology*,
1938, 30 128 139
- 19 JEFFERY, G M et al
Exo-erythrocytic stages of *Plasmodium fal-
ciparum* *Amer J trop Med Hyg* 1952,
1, 917 926
- 20 MUDROW, L
Klinische und parasitologische Befunde
und chemotherapeutische Ergebnisse bei
der Hühnermalaria *Arch Schiffs u
Tropenhyg* 1940, 44 257 275
- 21 RAFFAELI, G
Un ceppo italiano di *Plasmodium elon-
gatum* *Riv Malar* 1934, 13 332 337
- 22 SCHAUDINN F
Studien über krankheitsserregende Proto-
zoen II *Plasmodium vivax* (Grassi &
Feletti), der Erreger des Tertianfiebers
beim Menschen *Arch Gesundheitsw (Berl)*,
1902, 19, 169 250
- 23 SCHULEMANN, W
Synthetic anti malarial preparations *Proc
roy Soc Med* 1932, 25, 897 905
- 24 SHANNON, J A et al
The pharmacological basis for the rational
use of atabrine in the treatment of malaria
J Pharmacol 1944, 81, 307 330
- 25 SHORTT, H E et al
The pre-erythrocytic stage of human ma-
laria, *Plasmodium vivax* *Brit med J*
1948, 1, 547
- 26 SHORTT, H E et al
The pre-erythrocytic stage of *Plasmodium
falciparum* *Brit med J* 1949, 2, 1006-1008
- 27 SHORTT, H E et al
The pre-erythrocytic stage of *Plasmodium
falciparum* *Trans roy Soc trop Med
Hyg* 1951, 44, 405-419
- 28 SHORTT, H E, BRAY, R S &
COOPER, W
Further notes on the tissue stages of *Plas-
modium cynomolgi* *Trans roy Soc trop
Med Hyg* 1954, 48, 122 131
- 29 SHORTT, H E, GARNHAM P C C
& MALAMOS, B
The pre-erythrocytic stage of mammalian
malaria *Brit med J* 1948, 1, 192 194
- 30 SHORTT, H E, MENON, K P &
IYER, P V S
The form of *Plasmodium gallinaceum*
present in the incubation period of the
infection *Indian J med Res* 1940, 28
273 276
- 31 SMITH, J A & BIRD, W
Studies in malaria, with special reference
to treatment Part IX Plasmoquine in the
treatment of malaria *Indian J med Res*
1928, 16, 159 177
- 32 WOODWARD, R B & DOERING, W E
The total synthesis of quinine *J Amer
chem Soc* 1944, 66, 849

Individual Compounds on Use

venous and in
ion med Gaz

Quinine

- 33 CHOPRA, R N, ROY, A C & DAS
GUPTA, B M
On the concentration of quinine in the

- 34 COATNEY, G R et al
Studies in human malaria VII The protective and therapeutic action of quinine sulfate against III Elizabeth strain vivax malaria *Amer J Hyg* 1948, 47, 120-134
- III COGGESHALL, L T & CRAIG, B
Old and new plasmodicides In Boyd, M F, ed *Malariaology*, Philadelphia, Saunders, 1949, vol 2, pp 1071-1113
- 36 EARLE, D P jr et al
Studies on the chemotherapy of the human malaras II Method for the quantitative assay of suppressive antimalarial action in falciparum malaria *J clin Invest* 1948, 27, No 3, Part II, pp 75-79
- 37 SHANNON, J A et al
Studies on the chemotherapy of the human malaras I Method for the quantitative assay of suppressive antimalarial action in vivax malaria *J clin Invest* 1948, 27, No 3, Part II, pp 66-74
- 38 TAGGART, J V et al
Studies on the chemotherapy of the human malaras III The physiological disposition and antimalarial activity of the cinchona alkaloids *J clin Invest* 1948, 27, No 3, Part II, pp 80-86
- 39 WINCKEL, Ch W P
Quinine injections in malaria *J trop Med Hyg* 1947, 50, 201-203
- Primaquine and other 8-aminoquinolines
- 40 ALVING, A S et al
Korean vivax malaria II Curative treatment with pamaquine and primaquine *Amer J trop Med Hyg* 1953, 2, 970-976
- 41 ALVING, A S, ARNOLD, J & ROBINSON, H H
Status of primaquine 1 Mass therapy of subclinical vivax malaria with primaquine *J Amer med Ass* 1952, 149, 1558-1562
- 42 CLAYMAN, C B et al
Status III primaquine 3 Toxicity of primaquine in Caucasians *J Amer med Ass* 1952, 149, 1563-1568
- 43 COATNEY, G R et al
Korean vivax malaria V Cure of the infection by primaquine administered during long term latency *Amer J trop Med Hyg* 1953, 2, 985-988
- 44 COOPER, W C et al
Studies in human malaria XXXI Comparison of primaquine, isopentaquine, SN-3883, and pamaquine as curative agents against Chesson strain vivax malaria *Amer J trop Med Hyg* 1953, 2, 949-957
- 45 DI LORENZO, A et al
Korean vivax malaria IV Curative effect of 15 milligrams of primaquine daily for 7 days *Amer J trop Med Hyg* 1953, 2, 983-984
- 46 EARLE, D P jr et al
Studies on the chemotherapy of the human malaras IX Effect of pamaquine on the blood cells of man *J clin Invest* 1948, 27, No 3, Part II, pp 121-129
- 47 EDWARDS, J H et al
Primaquine, SN 13272, a new curative agent in vivax malaria a preliminary report *J nat Malar Soc* 1950, 9, 285-292
- 48 GARRISON, P L et al
Status of primaquine 2 Cure of Korean vivax malaria with pamaquine and primaquine *J Amer med Ass* 1952, 149, 1562-1563
- 49 HOCKWALD, R S et al
Status of primaquine 4 Toxicity of primaquine in Negroes *J Amer med Ass* 1952, 149, 1568-1570
- 50 JONES, R jr et al
Korean vivax malaria III Curative effect and toxicity of primaquine in doses from 10 to 30 mg daily *Amer J trop Med Hyg* 1953, 2, 977-982
- 51 SCHMIDT, I G & SCHMIDT, L H
Neurotoxicity of the 8-aminoquinolines III The effects of pentaquine, isopentaquine, primaquine, and pamaquine on the central nervous system of the rhesus monkey *J Neuropath* 1951, 10, 231-256
- 52 THAYER, A D jr, ARNOLD, J & ALVING, A S
A clinical study of primaquine (SN 13,272) in the treatment of malaria among

- the Miskito Indians of Nicaragua *Amer J trop Med Hyg* 1953, 2, 989-999
- 53 ZUBROD, C G, KENNEDY, T J & SHANNON, J A
Studies on the chemotherapy of the human malarial VIII The physiological disposition of pamaquine *J clin Invest* 1948, 27, No 3, Part II, pp 114-120
See also No 31
- Mepacrine**
- 54 BAKER, B M & PLATT, D
Vivax relapse rates following continued atabrine suppressive medication observations on malaria in an infantry regiment *Bull Johns Hopk Hosp* 1947, 81, 293-304
- 55 BANG, F H et al
Treatment of acute attacks of vivax and falciparum malaria: a comparison of atabrine and quinine *Bull US Army med Dep* 1947, 7, 75-80
- 56 BRODIE, B B et al
The estimation of basic organic compounds in biological material II Estimation of fluorescent compounds *J biol Chem* 1947, 168, 311-318
- 57 COOPER, W C et al
Studies in human malaria VIII The protective and therapeutic action of quinacrine against St Elizabeth strain vivax malaria *Amer J Hyg* 1949, 49, 25-40
- 58 ENGEL, G L, ROMANO, J & FARRIS, E B
Effect of quinacrine (atabrine) on the central nervous system, clinical and electroencephalographic studies *Arch Neurol Psychiat (Chicago)*, 1947, 58, 337-350
- 59 FAIRLEY, N H et al
Atabrine susceptibility of the Aitape-Wewak strains of *P falciparum* and *P vivax*—A field and experimental investigation by L H Q Medical Research Unit, Cairns *Trans roy Soc trop Med Hyg* 1946, 40, 229-273
- 60 FINDLAY, G M
The toxicity of mepacrine in man *Trop Dis Bull* 1947, 44, 763-779
- 61 FINDLAY, G M, MARKSON, J L & HOLDEN, J R
Investigations in the chemotherapy of malaria in West Africa III—Further investigations on treatment with quinine and mepacrine *Ann trop Med Parasit* 1944, 38, 201-204
- 62 GORDON, H H, CHRISTIANSON, H B & LIPPINCOTT, E W
A comparison of quinine and quinacrine in the treatment of the clinical attacks of vivax malaria *Sih med J (Bgham, Ala)*, 1946, 39, 631-634
- 63 HERING, E R, PATT, H M & LEAVITT, H J
Tolerability studies of some new anti-malarial drugs *J nat Malar Soc* 1948, 7, 322-329
- 64 LIVINGOOD, C S & DIEZUAIDE, F R
Untoward reactions attributable to atabrine *J Amer med Ass* 1945, 129, 1091-1093
- 65 LONDON, I M et al
The effects of quinacrine (atabrine) suppression on the course of Pacific vivax malaria *Amer J Med* 1946, 1, 615-620
- 66 MACHELLA, T E, KROMELMAN, L J & LEWIS, R A
The intravenous administration of atabrine in falciparum malaria *Bull US Army med Dep* 1947, 7, 1009-1021
- 67 MOST, H & HAYMAN, J M jr
Relative efficiency of quinacrine (atabrine) and quinine in treatment of acute attacks of vivax malaria *Amer J med Sci* 1946, 211, 320-324
- 68 PULLMAN, T N et al
Comparison of chloroquine, quinacrine (atabrine), and quinine in the treatment of acute attacks of sporozoite induced vivax malaria (Chesson strain) preliminary report *J clin Invest* 1948, 27, No 3, Part II, pp 46-50
- 69 TAGGART, J V et al
Studies on the chemotherapy of the human malarial V The antimalarial activity of quinacrine *J clin Invest* 1948, 27, No 3, Part II, pp 93-97

- 70 UNITED STATES OF AMERICA, ARMORED MEDICAL RESEARCH LABORATORY, FORT KNOX, KY & COMMISSION ON TROPICAL DISEASES, ARMY EPIDEMIOLOGICAL BOARD, PREVENTIVE MEDICINE SERVICE, OFFICE OF THE SURGEON GENERAL, U.S. ARMY Plasma quinine concentration as a function of dosage and environment *Arch Intern Med* 1946, 78, 64-107
71. WATKINS, R. C. & GHOSH, B. N. Quantitative and qualitative methods for detection of Atebrin in urine *Rec Malar Surv India*, 1934, 4, 367-390
- 71a WELCH, W. J. et al Syphilis of the central nervous system effect of quinine hydrochloride on the incidence of convulsions *Arch Derm Syph (Chicago)*, 1948, 57, 868-872
See also No 7, 24
- Chloroquine and other 4-aminoquinolines
- 72 ALVING, A. S. et al Studies on the chronic toxicity of chloroquine (SN 7618) *J clin Invest* 1948, 27, No 3, Part II, pp 60-65
- 73 BERBERIAN, D. A. & DENNIS, E. W. Field experiments with chloroquine diphosphate *Amer J trop Med* 1948, 28 755-776
- 74 BERLINER, R. W. et al Studies on the chemotherapy of the human malarial VI The physiological disposition, antimalarial activity, and toxicity of several derivatives of 4-aminoquinoline *J clin Invest* 1948, 27, No 3, Part II, pp 98-107
- 75 BRODIE, B. B. et al The estimation of basic organic compounds in biological material III Estimation by conversion to fluorescent compounds *J biol Chem* 1947, 168, 319-325
- 76 CHAUDHURI, R. N., RAI CHAUDHURI M. N. & CHAKRAVARTY, N. K. Chloroquine (SN 7618) in malaria *Indian J Malar* 1948, 2, 1-12
- 77 COATNEY, G. R. et al Studies in human malaria X The protective and therapeutic action of chloroquine (SN 7618) against St. Elizabeth strain vivax malaria *Amer J Hyg* 1949, 49, 49-59
- 78 CULWELL, W. B. et al Studies in human malaria XX The intramuscular administration of chloroquine *J nat Malar Soc* 1948, 7, 311-315
- 79 DECOURT, P. & SCHNEIDER, J. Traitement curatif du paludisme par divers sels du 3-méthyl-4 (diéthylaminopentyl) amino-7-chloroquinoline (Nivaquine) *Bull Soc Path exot* 1947, 40, 14-17
- 80 DOBROVOLNY, C. G., WHITE, W. C. & COATNEY, G. R. Chloroquine and chlorguanide as suppressants of malaria in Guatemala *Amer J trop Med Hyg* 1953, 2 805-845
- 81 GOLDSMITH, K. A controlled field trial of SN 7618 (chloroquine) for the suppression of malaria *J Malar Inst India* 1946, 6, 311-316
- 82 LOEB, R. F. et al Activity of a new antimalarial agent chloroquine (SN 7618) *J Amer med Ass* 1946 130, 1069-1070
- 83 MOST, H. et al Chloroquine for treatment of acute attacks of vivax malaria *J Amer med Ass* 1946 131, 963-967
- 84 PACKER, H. Experimental field type suppression with SN 7618 (chloroquine), SN 8137 and SN 12 837 (Paludrine) *J nat Malar Soc* 1947, 6 147-154
- 85 SCHMIDT, L. H. On the pharmacology of the 4-aminoquinolines In Wiggles, F. Y., ed *A survey of antimalarial drugs, 1941-1945*, Ann Arbor, Mich., Edwards, 1946, vol 1, pp 94-106
- 86 SCHNEIDER, J., LARANT, M. & BAILEY, M. Prophylaxe collective du paludisme par la Nivaquine Résultats de l'expérience de Chardimaou (Yunnan) *Bull Soc Path exot* 1945, 41, 188-194

87 SCHNEIDER, J & MÉCHALI, D

Traitement curatif du paludisme. Etude de l'activité comparée de quatre nouveaux dérivés synthétiques. *Bull Soc Path exot* 1948, 41, 274-282

88. YOUNG, M D & EYLES, D E

The efficacy of chloroquine, quinacrine, quinine and totaquine in the treatment of *Plasmodium malariae* infections (quartan malaria). *Amer J trop Med* 1948, 28, 23-28

See also No ■

Proguanil

89 ADAMS, A R D et al

Studies on synthetic antimalarial drugs XIII.—Results of a preliminary investigation of the therapeutic action of 4888 (Paludrine) on acute attacks of benign tertian malaria. *Ann trop Med Parasit* 1945, 39, 225-231

90 BRUCE CHWATT, L J & BRUCE-CHWATT, J M

Antimalarial drugs in West Africa with particular reference to proguanil. Results of a survey in Nigeria. *Brit med J* 1950, 2, 7-14

91 CARRINGTON, H C et al

A metabolite of Paludrine with high antimalarial activity. *Nature (Lond)*, 1951, 168, 1080

■ CIUCA, M et al

Trials of causal prophylaxis of malaria with Paludrine. *Bull Wild Hlth Org* 1948, 1, 297-300

93 COOPER, W C et al

Studies in human malaria XXVIII. Observations on the use of chlorguanide against the Chesson strain of *Plasmodium vivax*. *J nat Malar Soc* 1950, 9, 366-376

94 COVELL, G et al

Paludrine (proguanil) in prophylaxis and treatment of malarial infections caused by a West African strain of *P falciparum*. *Brit med J* 1949, 1, ■ 91

■ COVELL, G et al

Studies on a West African strain of *Plasmodium falciparum*. The efficacy of Palu-

drine (proguanil) as a prophylactic agent. *Trans roy Soc trop Med Hyg* 1949, 42, 341-346

96 COVELL, G et al

Studies on a West African strain of *Plasmodium falciparum*. II. The efficacy of Paludrine (proguanil) as a therapeutic agent. *Trans roy Soc trop Med Hyg* 1949, 42, 465-476

96a. CURD, F H S, DAVEY, D G & ROSE, F L

Studies in antimalarial drugs. X. Some biguanide derivatives as new types of antimalarial substances with both therapeutic and causal prophylactic activity. *Ann trop Med Parasit* 1945, 39, 208-216

97 EARLE, D ■ JR et al

Studies on the chemotherapy of the human malarial X. The suppressive antimalarial effect of Paludrine. *J clin Invest* 1948, 27, No 3, Part II, pp 130-133

98 EDISON, J F ■ & FIELD, J W

Proguanil resistant falciparum malaria in Malaya. *Brit med J* 1950, 1, 147-151

99. GAGE, J C & ROSE, F L

The estimation of Paludrine in urine. *Ann trop Med Parasit* 1946, 40, 333-336

100 GOOR, W TH VAN & LOBENS, J G

Clinical malaria prophylaxis with proguanil. *Docum neerl indones Morb trop* 1950, 2, 62-81

101 INNES, J R M

The effect of intramuscular injection of Paludrine and mepacrine in experimental animals. *Ann trop Med Parasit* 1947, 41, 46-49

102 JOHNSTONE, R ■ C

Relapsing benign tertian malaria treated with Paludrine. *Lancet*, 1946, 2, 825-826

103 JONES, R JR et al

The therapeutic effectiveness of large doses of Paludrine in acute attacks of sporozoite induced vivax malaria (Chesson strain). *J clin Invest* 1948, 27, No 3, Part II, pp 51-55

104 LINTS, H A et al

Studies in human malaria. XXII. Prolonged suppression of Chesson strain vivax

- malaria by the weekly administration of chloroquine or chloroquine J *nat Malar Soc.* 1950, 9, 50-58
105. MACKERRAS, M J & LECOLE, Q N Observations on the action of Paludrine on malarial parasites *Trans roy Soc trop Med Hyg* 1948, 41, 365-376
106. MAGEATH, M G et al The absorption and excretion of Paludrine in the human subject *Ann trop Med Parasit* 1946, 40, 493-506
107. MAGEATH, B G et al Paludrine in the treatment of malaria *Brit med J* 1946, 1, 903-905
108. MONK, J F Results of an investigation of the therapeutic action of Paludrine and pamaquin on acute attacks of benign tertian malaria *Trans roy Soc trop Med Hyg* 1948, 41, 657-662
109. MULLICK, K B & GUPTA, J C Intravenous Paludrine in malaria *Indian med Gaz* 1947, 82, 666-668
110. RAMAKRISHNAN, S P et al The effect of single and multiple doses of Paludrine upon *Plasmodium falciparum* *Amer J Hyg* 1952, 55, 239-245
111. RAY, A P Prophylactic use of Paludrine in a tea estate *Indian J Malar* 1948, 2, 35-66
112. SHUTE, P G & MARYON, M The gametocytocidal action of Paludrine upon infections of *Plasmodium falciparum* *Parasitology*, 1948, 38, 264-270
113. WILSON, T, MURDO, D S & RICHARD, D R Proguanil resistance in Malayan strains of *Plasmodium vivax* *Brit med J* 1952, 1, 564-568
See also No 8
- Pyrimethamine
114. ARCHIBALD, H M Preliminary field trials on a new schizonticide *Brit med J* 1951, 2, 821-822
115. BRUCE CHWATT, L J & ARCHIBALD, H M Field trials of new antimalarials in West Africa *Brit med J* 1953, 1, 539-541
116. COATNEY, G R et al Studies in human malaria XXXII The protective and therapeutic effects of pyrimethamine (Daraprim) against Chesson strain vivax malaria *Amer J trop Med Hyg* 1953, 2, 777-787
117. COVELL, G, SHUTE, P G & MARYON, M Pyrimethamine (Daraprim) as a prophylactic agent against a West African strain of *P falciparum* *Brit med J* 1953, 1, 1081-1083
118. COVELL, G SHUTE, P ■ & MARYON, M Pyrimethamine (Daraprim) in the treatment of vivax malaria *Brit med J* 1953, 2, 258-259
119. FOY, H & KONDI, A Effect of Daraprim on the gametocytes of *Plasmodium falciparum* *Trans roy Soc trop Med Hyg* 1952, 46, 370
120. GOODWYN, L G Daraprim (B W 50-63)—a new antimalarial trials in human volunteers *Brit med J* 1952, 1, 732-734
121. GOODWYN, L G Daraprim—Clinical trials and pharmacology *Trans roy Soc trop Med Hyg* 1952, 46, 485-495
122. HERNANDEZ, T et al Studies in human malaria XXXIV Acquired resistance to pyrimethamine (Daraprim) by the Chesson strain of *Plasmodium vivax* *Amer J trop Med Hyg* 1953, 2, 797-804
123. HITCHINGS, G H Daraprim as an antagonist of folic and folinic acids *Trans roy Soc trop Med Hyg* 1952, 46, 467-473
- 123a. JASWANT SINGH et al Acquired resistance to proguanil in *Plasmodium knowlesi* *Trans roy Soc. trop Med Hyg* 1952, 46, 639-649

- 123b JASWANT SINGH et al
Studies on the Nuri strain of *P. knowlesi*
V. Acquired resistance to pyrimethamine
Indian J. Malar. 1954, 8, 187-195
- 124 MYATT, A. V., HERNANDEZ, T. & COATNEY, G. R.
Studies in human malaria XXXIII The toxicity of pyrimethamine (Daraprim) in man *Amer. J. trop. Med. Hyg.* 1953, 2, 788-795
- 125 ROBERTSON, E. I., DAVEY, D. G. & FAIRLEY, N. H.
Cross resistance between Daraprim and proguanil *Brit. med. J.* 1952, 2, 1255-1256
- 126 ROLLO, I. M.
Daraprim—experimental chemotherapy *Trans. roy. Soc. trop. Med. Hyg.* 1952, 46, 474-484
- 127 SCHMIDT, L. H. & GENTHER, E. S.
The antimalarial properties of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine (Daraprim) *J. Pharmacol.* 1953, 107, 61-91
- 128 SCHMIDT, L. H., HUGHES, H. B. & SCHMIDT, I. H.
The pharmacological properties of 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine (Daraprim) *J. Pharmacol.* 1953, 107, 92-130
- 129 SCHNEIDER, J., CANET, J. & DUPOUX, R.
Traitement curatif du paludisme par une 2-4 diaminopyrimidine. Premiers résultats *Bull. Soc. Path. exot.* 1952, 45, 33-43
- 130 VINCKE, I. H.
Note préliminaire sur la prophylaxie médicamenteuse par Daraprim en milieu rural *Ann. Soc. belge Méd. trop.* 1952, 32, 91-99
- ### Drug-Resistance in Malaria
- 131 ADAMS, A. R. D. & SEATON, D. R.
Resistance to Paludrine developed by a strain of *Plasmodium falciparum* *Trans. roy. Soc. trop. Med. Hyg.* 1949, 42, 314-315
- 132 BISHOP, A. & BIRKETT, B.
Acquired resistance to Paludrine in *Plasmodium gallinaceum*, acquired resistance and persistence after passage through the mosquito *Nature (Lond.)*, 1947, 159, 884-885
- 133 BISHOP, A. & BIRKETT, B.
Drug resistance in *Plasmodium gallinaceum* and the persistence of Paludrine-resistance after mosquito transmission *Parasitology*, 1948, 39, 125-137
- 134 BISHOP, A. & McCONNACHIE, E. W.
Resistance to sulphadiazine and Paludrine in the malaria parasite of the fowl (*P. gallinaceum*) *Nature (Lond.)*, 1948, 162, 541-543
- 135 BISHOP, A. & McCONNACHIE, E. W.
The stability of Paludrine resistance in *Plasmodium gallinaceum* in the absence of the drug *Parasitology*, 1950, 40, 159-162
- 136 BISHOP, A. & McCONNACHIE, E. W.
Sulphadiazine resistance in *Plasmodium gallinaceum* and its relation to other antimalarial compounds *Parasitology*, 1950, 40, 163-174
- 137 BISHOP, A. & McCONNACHIE, E. W.
Cross resistance between sulphamamide and Paludrine (proguanil) in a strain of *Plasmodium gallinaceum* resistant to sulphamamide *Parasitology*, 1950, 40, 175-178
- 138 BISHOP, A. & McCONNACHIE, E. W.
Failure to produce resistance to chloroquine in *Plasmodium gallinaceum* in chicks *Parasitology*, 1952, 42, 52-56
- 139 BISHOP, A. & McCONNACHIE, E. W.
Pamaquin resistance in a strain of *Plasmodium gallinaceum* and its relationship to other antimalarial drugs *Parasitology*, 1952, 42, 57-64
- 140 BOYD, M. F.
On strains or races of the malaria parasites *Amer. J. trop. Med.* 1940, 20, 69-80
- 140a. CANET, J.
Proguanil resistance during mass prophylaxis of hyperendemic *P. falciparum* malaria in Indo China *Bull. Soc. Path. exot.* 1953, 46, 230-245

- 140b CHAUDHURI, R N & RAI CHAUDHURI, M N
Falciparum infection refractory to Paludrine *Indian J Malar* 1949, 3, 365-369
141. COOPER, W C, COATNEY, E R & IMBODEN, C A Jr
Studies in human malaria XXIII Acquired resistance to chloroquine in the Cheeson strain of *Plasmodium vivax* *J nat Malar Soc* 1950, 9, 59-66
142. FLETCHER, W
Notes on the treatment of malaria with the alkaloids of cinchona, London, Bale & Danielsson 1923 (Studies from the Instituto for Medical Research, Federated Malay States No 18)
- 143 FULTON, J E & YORKE, W
Studies in chemotherapy XXIX—The development of plasmoquine resistance in *Plasmodium knowlesi* *Ann trop Med Parasit* 1941, 35, 233-239
- 144 FULTON J D & YORKE W
Studies in chemotherapy XXXII—Further observations on plasmoquine-resistance in *Plasmodium knowlesi* *Ann trop Med Parasit* 1943, 37, 41-47
- 144a. GILROY, A B
Proguanil resistant *Plasmodium falciparum* in Assam *Ann trop Med Parasit* 1952 46 121-126
- 145 GREENBERG, J
Inhibition of the antimalarial activity of chloroquine by pteroylglutamic acid *Proc Soc exp Biol (NY)*, 1949, 71, 306-308
- 146 HAWKING E & PERRY, W L M
Resistance to proguanil (Paludrine) in a mammalian malaria parasite (*Plasmodium cynomolgi*) *Lancet*, 1948, 2, 850
- 147 HAWKING, E & THURSTON J E
A strain of monkey malaria (*Plasmodium cynomolgi*) made resistant to proguanil (Paludrine) *Trans roy Soc trop Med Hyg* 1951, 44 695-701
- 148 JAMES S P, NICOL, W D & SMYTH, P G
A study of induced malignant tertian malaria *Proc roy Soc Med* 1932, 25, 1153-1186
- 148a. JASWANT SINGH et al
Drug resistance of pro-erythrocytic forms of *Plasmodium gallinaceum* Brumpt, 1935 *Indian J Malar* 1952, 6, 457-464
- 148b JASWANT SINGH et al
Development of resistance to pyrimethamine in *P. cynomolgi* *Indian J Malar* 1953, 7, 357-368
- 149 JONES, E A
Experiment to determine if a proguanil resistant strain of *P. falciparum* would respond to large doses of pyrimethamine *Brit med J* 1953, 1, 977
- 150 JONES, S A
Resistance of *P. falciparum* and *P. malariae* to pyrimethamine (Daraprim) following mass treatment with this drug A preliminary note *E Afr med J* 1954, 31, 47-49
- 151 KNOPPERS, A Th
Acquired resistance (twofold) to quinine in *Plasmodium gallinaceum* *Nature (Lond)*, 1947, 160, 606-607
152. KOSSIAKOFF, M G
De la propriété que possèdent les microbes de s'accommoder aux milieux antiseptiques *Ann Inst Pasteur* 1887, 1, 465-476
- 153 LOURIE, E M
Studies on chemotherapy in bird malaria IV—Failure to promote drug resistance in *Plasmodium cathemerium* by prolonged administration of quinine or Plasmochin *Ann trop Med Parasit* 1935, 29, 421-433
- 154 McCONNACHIE, E W
Latent infections in avian malaria in relation to the production of drug resistance *Parasitology*, 1950 41, 110-116
- 155 MASSART, J
Sensibilité et adaptation des organismes à la concentration des solutions salines *Arch Biol (Paris)* 1889 9 515-570
- 156 NAUCK, E G
Chemotherapeutische Versuche bei Affenmalaria (*P. knowlesi*) *Arch Schiffs- u Tropenhyg* 1934 38 313-326

157. ROLLO, I M
A 2,4-diamino pyrimidine in the treatment of proguanil resistant laboratory malarial strains *Nature (Lond)*, 1951, 168, 332-333
158. ROLLO, I M
Daraprim resistance in experimental malarial infections *Nature (Lond)*, 1952, 170, 415
159. ROLLO, I M, WILLIAMSON, J & LOURIE, E M
Acquired Paludrine resistance in *Plasmodium gallinaceum* II—Failure to produce such resistance by prolonged treatment of latent infections *Ann trop Med Parasit* 1948, 42, 241-248
160. SCHMIDT, L H et al
Development of resistance to chloroquine (Paludrine) during treatment of infections with *Plasmodium cynomolgi* *J Pharmacol* 1949, 95, 382-398
161. SEATON, D R
Failure to induce chloroquine-resistance in *Plasmodium gallinaceum* *Ann trop Med Parasit* 1951, 45, 99-100
162. SEATON D R & ADAMS A R D
Acquired resistance to proguanil in *Plasmodium falciparum* *Lancet* 1949, 2, 323-324
163. SEATON D R & LOURIE, E M
Acquired resistance to proguanil (Paludrine) in *Plasmodium vivax* *Lancet* 1949, 1, 394-395
164. SHANNON J A et al
Studies on the chemotherapy of the human malarias. I Method for the quantitative assay of suppressive antimalarial action in vivax malaria *J clin Invest* 1948, 27, No 3 Part II pp 66-74
165. SINGH, J et al
Daraprim (5063) in simian malaria *Indian J Malar* 1951, 5, 531-540
166. THOMPSON, E E et al
On the ability of *Plasmodium lophurae* to acquire resistance to chloroquine, Camoquin and chloroquine *J infect Dis* 1948, 83, 250-255
167. WALKER, A J & REID, J A
Resistance to proguanil in the gametocytes and pre-erythrocytic forms of *Plasmodium falciparum* *Trans roy Soc trop Med Hyg* 1953, 47, 580
168. WILLIAMSON, J, BERTRAM, D S & LOURIE, E M
Effects of Paludrine and other antimalarials *Nature (Lond)*, 1947, 159, 885-886
169. WILLIAMSON, J & LOURIE, E M
Acquired Paludrine resistance in *Plasmodium gallinaceum* I—Development of resistance to Paludrine and failure to develop resistance to certain other anti-malarials *Ann trop Med Parasit* 1947, 41, 278-291
170. WILSON, T & EVESON J F B
Treatment of acute malaria with pyrimethamine *Brit med J* 1953, 1, 253-255
171. WILSON, T, MUNRO, D S & RICHARD, D R
Proguanil resistance in Malayan strains of *Plasmodium vivax* *Brit med J* 1952, 1, 564-568
172. WORK, T S & WORK, H
The basis of chemotherapy, Edinburgh, Oliver & Boyd, 1948
173. YUDKIN J
Origin of acquired drug resistance in bacteria *Nature (Lond)*, 1953, 171, 541-546
See also No 8, 37, 59, 98, 100, 105, 110, 112, 122, 125, 127

Clinical Use of Antimalarial Drugs

174. GREAT BRITAIN, COLONIAL MEDICAL RESEARCH COMMITTEE, MALARIA SUBCOMMITTEE
Use of antimalarial drugs. Recommendations *Lancet* 1954, 1, 1340-1342
175. JELLIFFE, H H & JELLIFFE, E F H
The out patient treatment of malaria with single dose intramuscular chloroquine in a hyperendemic area in West Africa *Trans roy Soc trop Med Hyg* 1953, 47, 235-238

176. MOHR, W
Parenterale Resochanthérapie bei den verschiedenen Malariaformen *Z Tropenmed Parasit* 1953, 4 137 153
177. PAYNE, E H et al
Intravenous amodiaquin (Camoquin) in naturally acquired and induced malaria
Amer J trop Med 1951 31, 698 702
178. PAYNE E H, SHARP, A E & NICKEL, K C
Parenteral use of Camoquin hydrochloride as an antimalarial *Amer J trop Med* 1949 29, 353 368
179. RANSOME, G A
Notes on the management of cases of cerebral malaria *Proc Alumni Ass King Edw VII Coll Med* 1948, 1 23 28
180. SCOTT, V
Single intravenous injections of chloroquine in the treatment of falciparum malaria toxic and immediate therapeutic effects in 110 cases *Amer J trop Med* 1950, 30, 503 510
181. SPICKNALL, C O, TERRY, L L & COATNEY G R
The treatment of falciparum malaria with intramuscular chloroquine *Amer J med Sci* 1949 218 374-377
182. STRAHAN, J H
Quinine by continuous intravenous drip in the treatment of acute falciparum malaria *Trans roy Soc trop Med Hyg* 1948, 41, 669-676
See also No 31 39 40, 43, 44, 50, 116, 117

INDEX

INDEX

- Absorption and elimination of drugs, *see* under *specific drugs*
- Acridine derivatives, *see* 9-Aminoacridines
- Activity of drugs, *see* under *specific drugs*
- Acute infection, simple, treatment, 74-77
- Administration of drugs, *see* under *specific drugs*
- After treatment, 84-85
 - falciparum infection, 84
 - vivax infection, 85
- Age and body-weight in dosage, 73
- 9-Aminoacridines, chemical structure, ■■
 - See also* Mepacrine
- 4-Aminoquinolines, activity, 71
 - chemical structure, 19
 - dosage, grave infection, 78
 - simple acute infection, 74
 - historical aspects, 13
 - use in recrudescing falciparum infection, 81
 - See also* Amodiaquine, Chloroquine, Sontoquine
- 8-Aminoquinolines, activity, 71
 - chemical structure, 17
 - for radical cure of vivax infection, ■■ 83
 - historical aspects, 14
 - use in relapsing vivax infection, 82
 - See also* Pamaquine, Primaquine
- Amodiaquine, activity, 71
 - administration, route, 80
 - advantages over mepacrine, 43
 - base-content of tablets, 99
 - chemical structure, ■■
 - dosage, suggested, summary, 97 98
 - for collective prophylaxis, 91
 - for emergency control of epidemics, 92
- Amodiaquine (*continued*)
 - for general protection, 87, ■■
 - in grave infection, 78, 80
 - in simple acute infection, 74, 76
 - resistance, 58
 - salts, physical data, 100
 - single-dose therapy for dispensary patients, ■■
 - synonyms, 101
- Antibiotics, antimalarial activity, 23
- Antimalarial drugs, absorption and elimination, *see* under *specific drugs*
 - action on life-cycle of parasite, 26-27, 70
 - activity, *see* under *specific drugs*
 - administration, *see* under *specific drugs*
 - chemical structure, 16-23
 - clinical use, 69 93
 - concentration in body fluids, factors affecting, 27 28
 - cross-resistance, 64-65
 - historical review, 10-14
 - pharmacology, 27 ■■
 - resistance, 54-68, 73
 - spelling of names, 10
 - synonyms, 101
 - synthetic, evolution, 11
 - toxicity, *see* under *specific drugs*
 - types forming basis of present-day therapy, 71
- Asexual blood forms, *see* Erythrocytic forms, asexual
- Asexual parasitaemia, effect of quinine on, 33
- Base of salt, confusions ■■ dosage, 73
- Base-content of tablets, 99
 - recommended use in expressing dosage, 73
- Basic drugs for present-day therapy, 71

- Biguanides, activity, 71
chemical structure, 20
See also Proguanil
- Biological approach to research, 23 31
- Blackwater fever, malaria parasites in early stages, 85
- Body weight and age in dosage, 73
- Carriers, symptomless, *see* Symptomless carriers
- Causal prophylaxis, ■
- Chemical approach to research, 15-23
- Chloroquine, 43-46
absorption and elimination, 44
activity in human malaria, 43, 71
administration, route, 78, ■
advantages over mepacrine, 43
base-content of tablets, 99
chemical structure, 19
contraindications, 44
dosage, suggested, summary, 97-98
estimation in body fluids, 45-46
for collective prophylaxis, 91
for emergency control of epidemics, 92
for general protection, 87, 88
in grave infection, 77, 78, ■
in simple acute infection, 74, 76
plasma concentrations during treatment, 44
resistance, 57
salts in common use, 46
physical data, 100
single-dose therapy for dispensary patients, 84
synonyms, 101
toxicity, 44
- Cinchona, historical aspects, 10
- Cinchona alkaloids, chemical structure, 16
See also Quinine
- Cinchona mixtures, 36
- Clinical attack, non immune subjects, suggested dosage, 97
semi immune subjects, suggested dosage, 98
- Clinical cure, definition, 9
- Clinical use of antimalarial drugs, 69 93
- Collective drug prophylaxis, 89-93
dosage of various drugs, 90 92
indications, 91
limitations, ■
- Collective drug prophylaxis (*continued*)
principles, 92
role in control of epidemics, 92
- Confusions of dosage, 72-74
- Control of epidemics, role of collective drug prophylaxis, 92
- Cross resistance between antimalarial drugs, 64-65
- Cure, definition, 9
radical, malariae infection, 97
vivax infection, 82 83, 97
- Diaminopyrimidines, chemical structure, 21
See also Pyrimethamine
- Dispensary patients, mepacrine and quinine dosage, 84
recommended treatment, 83 84
single dose therapy, 84
- Dosage, age and body weight in, 73
confusions, 72 74
summary, 97-98
clinical attack, 97, 98
emergency treatment, 97
prophylaxis and suppression, 98
radical cure, vivax and malariae infections, 97
- Drug resistance, 54 ■
acquired by previous drug contact, 56
definition, 55
in geographical strains, 56
natural, within species, 53
nature, 67
origin and mechanism, 65-66
range, 57
relation to confusions of dosage, 73
See also under specific drugs
- Drugs, antimalarial, *see* Antimalarial drugs
- Emergency treatment, suggested dosage, 97
- Epidemics, control, role of collective drug prophylaxis, 92
- Erythrocytic forms, asexual, drugs acting on, 27, 32, 37, 39, 43, 47, 51
resistance to proguanil, 47, 59 60
- Exoerythrocytic forms, primary, *see* Pre-erythrocytic forms
resistance to proguanil, 59
secondary, drugs acting on, 27, 37, 51

- Falciparum infection after treatment 84
- Fever in acute malaria effect of quinine on 33
- Gametocytes drugs acting on 27 37 39
 - 43, 48 52
 - resistance to proguanil 60
- Gametocytocide definition 9
- General protection dosage of various drugs 87 91 98
- Grave infection treatment 77-81
- Historical review of antimalarial drugs 10-14
- Immunity factor effect on dosage 72
- necessity for research on 29
- Individual drug prophylaxis 86-89
- causal 88
- for general protection 87
- side-effects 88 89
- Lapinone, chemical structure 22
- suppressive action against vivax malaria 22
- Life-cycle of malaria parasite 23 26
- action of drugs on 26 27 70
- development in blood stream and tissues 24 25
- Loading dose in treatment of acute simple infection 75
- Malaria parasite *see* Parasite
- Malariae infection radical cure 97
- Mepactrine 39-42
 - absorption and elimination 40
 - activity in human malaria 39 71
 - administration route 78 80
 - advantages over quinine 40
 - base-content of tablets 99
 - chemical structure 18
 - contraindications 40
 - dosage suggested summary 97 98
 - estimation in body fluids 41
 - for collective prophylaxis 91
 - for dispensary patients 84
 - for emergency control of epidemics 92
 - for general protection 87 88
 - historical aspects 12 13
 - in grave infection 77 78 80
- Mepactrine (*continued*)
 - in simple acute infection 74 76
 - plasma concentrations during treatment 40-41
 - resistance 57
 - salts in common use 42
 - physical data 100
 - synonyms 101
 - toxicity 40
- Metachlorindone chemical structure 70
- Miscellaneous compounds antimalarial activity 23
- Naphthoquinones activity against avian plasmodia 22
- chemical structure 22
- Organometallic compounds antimalarial activity 22 23
- Pamaquine activity 71
- base-content of tablets 99
- chemical structure 17
- dosage radical cure of vivax infection 83
- suggested summary 97 98
- historical aspects 12 13
- resistance 57
- salts physical data 100
- synonyms 101
- Parasite life-cycle 23 27 70
- resistance to drugs *see* Drug resistance
- response of different strains to drugs 28 29 72
- See also under specific forms of parasite*
- Pharmacology of antimalarial drugs 27 28
- Plasma concentrations *see under specific drugs*
- Plasmodium metabolism effect of drugs on 30
- Pre-erythrocytic forms demonstration in monkeys liver 24 25
- drugs acting on 26 37 47 51
- Primaquine 37 39
 - absorption and elimination 38
 - activity in human malaria 37 71
 - base-content of tablets 99
 - chemical structure 18
 - contraindications 38
 - dosage radical cure of vivax infection 83

- Biguanides, activity, 71
 chemical structure, 20
 See also Proguanil
- Biological approach to research, 23 31
- Blackwater fever, malaria parasites in early stages, 85
- Body-weight and age in dosage, 73
- Carriers, symptomless, *see* Symptomless carriers
- Causal prophylaxis, 88
- Chemical approach to research, 15 23
- Chloroquine, 43-46
 absorption and elimination, 44
 activity in human malaria, 43, 71
 administration, route, 78, 80
 advantages over mepacrine, 43
 base content of tablets, 99
 chemical structure, 39
 contraindications, 44
 dosage, suggested, summary, 97-98
 estimation in body fluids, 45-46
 for collective prophylaxis, 91
 for emergency control of epidemics, 92
 for general protection, 87, 88
 in grave infection, 77, 78, 80
 in simple acute infection, 74, 76
 plasma concentrations during treatment, 44
 resistance, 57
 salts in common use, 46
 physical data, 100
 single dose therapy for dispensary patients, 84
 synonyms, 101
 toxicity, 44
- Cinchona, historical aspects, 10
- Cinchona alkaloids, chemical structure, 16
 See also Quinine
- Cinchona mixtures, 36
- Clinical attack, non-immune subjects, suggested dosage, 97
 semi immune subjects, suggested dosage, 98
- Clinical cure, definition, 9
- Clinical use of antimalarial drugs, 69-93
- Collective drug prophylaxis, 89 93
 dosage of various drugs, 90 92
 indications, 91
 limitations, 89
- Collective drug prophylaxis (*continued*)
 principles, 92
 role in control of epidemics, 92
- Confusions of dosage, 72-74
- Control of epidemics, role of collective drug prophylaxis, 92
- Cross-resistance between antimalarial drugs, 64 65
- Cure, definition, 9
 radical, malariae infection, 97
 vivax infection, 82 83, 97
- Diaminopyrimidines, chemical structure, 21
 See also Pyrimethamine
- Dispensary patients, mepacrine and quinine dosage, 84
 recommended treatment, 83-84
 single dose therapy, 84
- Dosage, age and body weight in, 73
 confusions, 72 74
 summary, 97 98
 clinical attack, 97, 98
 emergency treatment, 97
 prophylaxis and suppression, 98
 radical cure, vivax and malariae infections, 97
- Drug-resistance, 54 68
 acquired by previous drug contact, 56
 definition, 55
 in geographical strains, 56
 natural, within species, 55
 nature, 67
 origin and mechanism, 65 66
 range, 57
 relation to confusions of dosage, 73
 See also under specific drugs
- Drugs, antimalarial, *see* Antimalarial drugs
- Emergency treatment, suggested dosage, 97
- Epidemics, control, role of collective drug prophylaxis, 92
- Erythrocytic forms, asexual, drugs acting on, 27, 32, 37, 39, 43, 47, 51
 resistance to proguanil, 47, 59 60
- Exoerythrocytic forms, primary, *see* Pre-erythrocytic forms
 resistance to proguanil, 59
 secondary, drugs acting on, 27, 37, 51

- Single-dose therapy for dispensary patients, 84
- Sontoquine, chemical structure, 19
historical aspects, 13
synonyms, 101
- Sporogonic forms, drugs acting on, 27
- Sporontocide, definition, 9
- Strain of parasite, relation to dosage, 72
- Sulfonamides, antimalarial activity, 19-20
See also Metachloridine
- Suppression, definition, 9
suggested dosage, 98
- Symptomless carriers, 85 86
and splenic enlargement, 86
"blood positive", 86
of latent vivax infection, 86
- Synergism, 29 30
- Synonyms of antimalarial drugs, 101
- Terms, definition, 9, 55
- Therapeutic policy, 70-71
- Toxicity of drugs, *see under specific drugs*
- Treatment, grave infection, 77-81
relapses, 81 82
simple acute infection, 74-77
- Vivax infection, after-treatment, 85
radical cure, 82 83, 97
suppressive action of Lapinone on, 22
- Weight-dosage, *see* Age and body-weight
in dosage
- Young's formula for body-weight dosage,
73
-

Primaquine (*continued*)

- suggested, summary, 97-98
- salts in common use, 39
- physical data, 100
- synonyms, 101
- toxicity, 38

Proguanil, 46-51

- absorption and elimination, 49
- activity in human malaria, 47-49, 71
- base-content of tablets, 99
- chemical structure, 21
- comparison with quinine for treatment of acute malaria, 48
- contraindications, 49
- dosage, suggested, summary, 97-98
- estimation in body fluids, 49
- evolution, 14
- for collective prophylaxis, 91
- for general protection, 87
- plasma concentrations during treatment, 49, 50
- resistance, 59-64
 - development in schizogonic blood forms, 47
 - prevention, 63
 - range, 59
 - rate of development, 60
 - recognition, 62
 - spread under field conditions, 61
 - stability, 61
- salts in common use, 50
 - physical data, 100
- synonyms, 101
- toxicity, 49

Prophylaxis, collective drug, see Collective drug prophylaxis

- definition, 9
- dosage of various drugs, 87, 90-92, 98
- individual drug, *see* Individual drug prophylaxis

Pyrimethamine, 51-53

- absorption and elimination, 53
- activity in human malaria, 51-52, 71
- chemical structure, 21-22
- contraindications, 52
- dosage, suggested, summary, 97-98
- effect on parasite rate, 51
- effect on sporozoite-rate, 52
- for causal prophylaxis in falciparum infection, 88
- for collective prophylaxis, 91
- for general protection, 87, 88

Pyrimethamine (*continued*)

- resistance, 58
- synonyms, 101
- toxicity, 52, 89

Pyrimidines, activity, 21

- chemical structure, 15
- See also* Pyrimethamine

Quinine, 32-37

- absorption and elimination, 34
- activity in human malaria, 32, 71
- and cinchona mixtures, 36
- administration, route, 78-79
- contraindications, 34
- detection in urine, 36
- dosage, suggested, summary, 97-98
- effect on asexual parasitaemia, 33
- effect on fever in acute malaria, 33
- for collective prophylaxis, 91
- for dispensary patients, 84
- for general protection, 87, 88
- in grave infection, 77, 78
- in simple acute infection, 74, 76
- isolation, 11
- plasma concentrations during treatment, 35
- resistance, 57
- salts in common use, 37
 - physical data, 100
- toxicity, 34

Quinoline derivatives, see 4-Aminoquinolines, 8-Aminoquinolines**Radical cure**, definition, 9

- malariae infection, 97
- vivax infection, 82-83, 97

Recrudescing infections, see Relapses**Relapses, causes**, 81

- treatment, falciparum infection, 81
- vivax infection, 82

Research, biological approach, 23-31

- chemical approach, 15-23

Resistance to antimalarial drugs, see Drug-resistance**Salts of antimalarial drugs, physical data**, 100**Schizontocides, definition**, 9**Sexual forms, see Gametocytes**

